CONTENTS

The American Journal of Medicine

Vol. XIII DECEMBER, 1952 No. 6

Editorial

Basis for Dietary Treatment in the Prevention and Control of Atherosclerosis
DAVID P. BARR 665

Clinical Studies

Quantitative Studies of Ascitic Fluid Circulation with Tritium-labeled Water
THEODORE C. PRENTICE, WILLIAM SIRI AND ETHEL E. JOINER 668

Using tritium-labeled water to study volume and turnover of the ascitic fluid in six patients with decompensated portal cirrhosis or peritoneal carcinomatosis, the authors find that movement of fluid in and out of the abdominal cavity is much more rapid than previously suspected: about 40 to 80 per cent of the total volume of ascitic fluid enters or leaves the peritoneal cavity each hour. A revised concept of the mechanisms of ascites formation is offered which does indeed give better insight into some of the clinical vagaries of fluid accumulation in the abdomen.

Experience with Needle Liver Biopsies at the Hepatitis Center for Japan and Korea, 1950–1951 . . CAPT. STEPHEN H. DESCHAMPS AND LT. COL. ARTHUR STEER 674

This paper summarizes the experience with needle liver biopsies in seventy-three patients at the Hepatitis Center currently established in Japan. The circumstances under which needle biopsy was found to be indicated or contraindicated are defined. The procedure helped materially in diagnosis and management in an impressive number of specific cases and a great deal of more general information was obtained in regard to the duration of active infection and the development of common and uncommon sequelae. This excellent report makes interesting and instructive reading.

An Evaluation of Needle Biopsy of the Liver . . . . . EDWARD R. CHRISTIAN 689

Dr. Christian's well documented experience demonstrates once again that despite its obvious limitations needle biopsy of the liver is a useful and reasonably safe procedure. The illustrations give graphic evidence of the range of diagnosis possible by this method.

Altered Liver Function of Chronic Congestive Heart Failure
JOHN M. EVANS, HYMAN J. ZIMMERMAN, J. GRANT WILMER, LAWRENCE J. THOMAS AND CLAYTON B. ETHRIDGE 704

This is a well rounded discussion of the results of the customary liver function tests in patients with congestive heart failure. Among contributory factors considered are the reduction in hepatic blood flow incidental to reduction in cardiac output, hypoxia, increased venous pressure and the possible effects of impaired inactivation of antidiuretic factors and of steroids.

Contents continued on page 5

NEW

prompt . . . prolonged . . .
prescribed relief of pain

APAMIDE

BRAND • TRADEMARK

tablets

(N-acetyl-p-aminophenol, 0.3 Gm.)

analgesic-antipyretic

rapid, direct analgesia

Apamide quickly relieves pain and reduces fever through direct analgesic-antipyretic action. It avoids the delay inherent in compounds that require metabolic transformation to produce analgesia.

prolonged relief of pain

Apamide goes to work fast. It raises the pain threshold substantially within 30 minutes, reaches peak effect in about 2½ hours and continues to be effective for approximately 4 hours.

well-tolerated analgesic

Apamide is a pure, active agent that does not produce extraneous, possibly toxic metabolites. High dosages over long periods have not been shown to cause toxic reactions or gastric upsets. It is extremely valuable in patients who cannot tolerate salicylates.

℞ only

Available only on your prescription, *Apamide* permits precise control of dosage and duration of treatment *by you*. Prescribe it for relief of pain and reduction of fever in respiratory infections, functional headache, muscular or joint pain and dysmenorrhea. Average adult dose, 1 tablet every four hours.

for a sedative-analgesic
prescribe

APROMAL

BRAND • TRADEMARK

tablets

(N-acetyl-p-aminophenol, 0.15 Gm. and acetylcarbromal, 0.15 Gm.)

non-narcotic, non-barbiturate

Apromal is especially valuable in those cases where pain coexists with tension, anxiety, restlessness, excitement, nervousness and irritability. *Apromal* contains Apamide and the widely used, gentle daytime sedative, acetylcarbromal. Enhancement of both analgesia and sedation is secured by this combination. Average adult dose, 1 tablet every 4 hours.

AMES

COMPANY, INC., ELKHART, INDIANA **Ames Company of Canada, Ltd., Toronto**

43332

CONTENTS

The American Journal of Medicine

Vol. XIII DECEMBER, 1952 No. 6

Contents continued from page 3

Early Roentgen Diagnosis in Massive Bleeding from the Upper Gastrointestinal Tract. I. Clinical Evaluation of Safety and Reliability of the Method in 123 Patients
NORMAN ZAMCHECK, THOMAS P. COTTER, SIMON E. HERSHORN, THOMAS C. CHALMERS, MAX RITVO AND FRANKLIN W. WHITE 713

This paper deals with a much disputed point—the propriety of and necessity for early roentgen examination in patients with brisk gastrointestinal hemorrhage. The authors demonstrate clearly that this can be done with impunity if suitable precautions are observed.

Blood Levels after Tracer Doses of Radioactive Iodine in the Diagnosis of Thyroid Disorders . . SOLOMON SILVER, MACK H. FIEBER AND STEPHEN B. YOHALEM 725

The authors have improved the diagnostic use of tracer doses of I^{131} by employing a windowless Q-gas counter to increase sensitivity and by measuring radioactivity of the blood seventy-two hours after oral administration of I^{131}, when there is an increase in radioactivity in hyperthyroid but not in euthyroid subjects. The results in a large series of cases are impressive and suggest further trial.

Reviews

Protein Flocculation Reactions. A Physico-chemical Approach . . ABRAHAM SAIFER 730

The protein flocculation tests, apart from their intrinsic interest, have come to play an important role in diagnosis. This review attempts to analyze the mechanisms involved in terms of physical chemistry and colloid, chemistry indicating the implications in respect to alterations of the serum proteins and lipids. The review as a whole adds much needed perspective to this growing field.

Current Principles of Management in Gout . ALEXANDER B. GUTMAN AND T. F. YÜ 744

Gout is due to a genetically determined inborn error of purine metabolism. While no cure is available, the consequences of the disorder can be minimized and counteracted effectively by applying the principles here set forth. These are oriented toward two more or less distinct problems presented by the disease; that of prevention and suppression of acute attacks, and that of prevention and mobilization of tophi. The use of colchicine, ACTH, phenylbutazone, benemid and diet for these purposes is described and the results analyzed.

Seminars on Gastrointestinal Physiology

Problems in Ulcerative Colitis . . . . . THOMAS E. MACHELLA 760

Dr. Machella contributes a critical discussion of current views as to the etiology and therapy of ulcerative colitis, giving consideration to both the colonic and extracolonic aspects of the disorder. He discusses in greater detail the special problems of emotional factors, pregnancy and carcinoma in ulcerative colitis. Finally, he takes up the vexing question of when in the course of the disease surgical intervention is indicated. The review as a whole gives good orientation in a complex and controversial subject.

Contents continued on page 7

Therapy for Vascular Headache to Reverse the Physiologic Disturbance

Headache, a problem encountered in all kinds of medical practice, may occur in association with any of a variety of disorders, some organic, others purely functional.

In headaches of organic etiology, e. g. sinusitis, febrile disease, brain abscess — the primary objective is to eliminate the basic disease. Head pain can be relieved temporarily with analgesics, pending diagnosis and definitive treatment.

Functional types of headache present a greater problem, because of the obscure nature of their etiology and their recurrent nature. Among these are:

Migraine (both classical and variant forms)
Tension headache
Psychogenic headache
Histaminic cephalgia

Wolff and his co-workers established that the pain of these headaches is due to disturbance of the tonus of cranial blood vessels — hence the term *vascular headaches.*

The craniovascular changes associated with the several phases of the typical migraine attack are:

Vasoconstriction (Drawing I) — to which the visual prodromata are attributable. It is possible to abort the attack during this phase in all but a few cases. (See treatment below.)

Vasodilatation (Drawing II) — as the vessels lose their tone, exaggerated pulsations set in, resulting in the throbbing pain which characterizes vascular headache. Treatment for the attack is still effective during this phase. (See below.)

Vessel Edema (Drawing III) — if the vasodilation continues for too long, vessel walls become edematous; this changes the character of the pain to a steady, intense aching. The attack can now no longer be checked, even with maximum dosage of specific drugs. *Moreover, sustained headache often induces reflex neck muscle tension, a source of residual pain.*

VESSEL STATE — ACCOMPANYING SYMPTOMS

I

PRIMARILY VISUAL DISTURBANCES: SCOTOMAS, HEMIANOPIA, UNILATERAL PARESTHESIA, PHOTOPHOBIA.

SPEECH DISORDERS AND MOOD CHANGES: THESE USUALLY LAST FROM A FEW MINUTES TO AN HOUR.

VASOCONSTRICTION

II

AGONIZING PERIODIC HEADACHE USUALLY LIMITED TO TEMPORAL, FRONTAL OR OCCIPITAL REGIONS.

HEADACHE IS THROBBING IN NATURE AND IS RELIEVED SOMEWHAT BY PRESSURE ON COMMON CAROTID ARTERY.

VASODILATATION

III

THE AGONIZING HEADACHE BECOMES DULL AND STEADY, MAY LAST FOR HOURS OR DAYS.

NAUSEA, VOMITING, DRYNESS OF MOUTH, EXCESSIVE SWEATING AND CHILLINESS MAY OCCUR DURING THIS STAGE.

EDEMA

Therapy: For maximum success, treatment must follow two lines:

1. Relieve the acute attack — of the numerous drugs which have been tried, ergotamine and its derivative preparations have proved most effective. The *newest product is oral tablets* of Cafergot®, N.N.R. (ergotamine with caffeine 'Sandoz'). When dosage is adjusted to the needs of the individual, Cafergot will give good relief in 85% of cases. It enables a greater number of patients to benefit from early administration since the oral route simplifies treatment as compared to parenteral therapy.

Many migraine patients delay taking medication until the attack has reached its height. Explicit dosage instructions may be forgotten unless the patient is made to realize their importance. To help encourage adherence to correct dosage procedure, Sandoz Scientific Department has prepared pads of INSTRUCTIONS as reproduced below.

For.....Date.....

1. Take 2 tablets at first sign of attack.
2. If the attack continues take one additional tablet every half-hour until attack is terminated.
3. Do not take more than 6 tablets for any single attack or more than 10 tablets in any one week.
4. If attack develops more rapidly or is more severe than usual, take 3 or 4 tablets as early as possible.
5. If you notice any change in your symptoms, report to your physician immediately.

.....M.D.

Do not take tablets between attacks.

2. Reduce the frequency of attacks — psychotherapy and regulation of living habits to avoid fatigue and nervous tension are most effective.

Supplies of Instruction Sheets as shown in facsimile above will gladly be sent on request; reprints of recent reports on Vascular headaches are also available.

GENERAL REFERENCES: DeJong, R.: Chicago M. Soc. Bull. *54*: 106, 1951. Friedman, A.: Modern Headache Therapy, St. Louis, C. V. Mosby Co., 1951. Shofstall, C. and Shofstall, W.: J. Kansas M. Soc. *52*: 366, 1951. Wolff, H.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

Sandoz Pharmaceuticals
DIVISION OF SANDOZ CHEMICAL WORKS, INC.
68 CHARLTON STREET, NEW YORK 14, N. Y.

CONTENTS

The American Journal of Medicine

Vol. XIII DECEMBER, 1952 No. 6

Contents continued from page 5

Clinic on Psychosomatic Problems

Hyperventilation in a Patient Who Stammered. Methedrine As an Adjunct to Psychotherapy 777

Clinic on Psychosomatic Problems (Massachusetts General Hospital)—This case report is of interest on several counts, particularly in relation to hyperventilation, a more common and troublesome manifestation of anxiety than is often appreciated. The use of D-desoxyephedrine to induce relaxation during an interview is worth noting.

Clinico-pathologic Conference

Aplastic Anemia in a Patient Receiving Chloramphenicol 782

Clinico-pathologic Conference (Washington University School of Medicine)—The principal subject of this conference deals with the current problem of chloramphenicol toxicity but, in addition, there is informative discussion of the more general aspects of bone marrow depression by drugs. The modern treatment of chronic prostatitis is also considered at some length.

Case Reports

Autoimmune Hemolytic Disease and Cryoglobulinemia Associated with Chronic Lymphocytic Leukemia. Hematologic and Metabolic Studies

ALBERT B. CRAIG, CHRISTINE WATERHOUSE AND LAWRENCE E. YOUNG 793

This case of chronic lymphocytic leukemia was carefully studied by hematologic and metabolic methods over a prolonged period before and during ACTH therapy. The discussion of the changes noted both in immune mechanisms and in balance studies during the course of observation is lucid and instructive.

Coarctation of the Aorta in Infancy. Report of Two Cases with Death from Left Ventricular Failure

H. MILTON ROGERS, COUNCILL C. RUDOLPH AND JOHN H. CORDES, JR. 805

Because of the availability of corrective surgical procedures, early diagnosis of coarctation of the aorta has assumed greater importance. The two cases reported bring out some helpful points in diagnosis.

Inspiratory-Expiratory Vital Capacity Test of Pulmonary Function . ALAN LESLIE 809

The author proposes a simple extension of the vital capacity test which gives information not afforded by the conventional technic, particularly in patients with bronchiolar narrowing or loss of elasticity of the lungs.

Author Index to Volume XIII 813

Subject Index to Volume XIII 816

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.

Great Potency

in tiny form

the therapeutic multivitamin tablet with B_{12} and no fish-oil taste

FOR potency and convenience, prescribe OPTILETS —the smallest tablet of its kind in therapeutic dose vitamins. Compressed, easy-to-swallow, OPTILETS contain therapeutic amounts of six synthetic vitamins plus B_{12}. Since there is no fish oil, there are no allergic reactions, no aftertaste, no "burp." Because OPTILETS are tablets—not capsules—they can't leak, won't stick together. Therapeutic dose is one or more daily. At pharmacies in bottles of 50, 100 and 1000. Cost no more than ordinary therapeutic formula vitamins.

Abbott

Specify **Optilets®**

(Abbott's Therapeutic Formula Vitamin Tablets)

Each OPTILET tablet contains:

→Vitamin A (synthetic)	25,000 U.S.P. units
Vitamin D (Viosterol)	1000 U.S.P. units
Thiamine Mononitrate	10 mg.
Riboflavin	5 mg.
Nicotinamide	150 mg.
→Vitamin B_{12} (as vitamin B_{12} concentrate)	6 mcg.
Ascorbic Acid	150 mg.

Actual Size

VI-PENTA DROPS

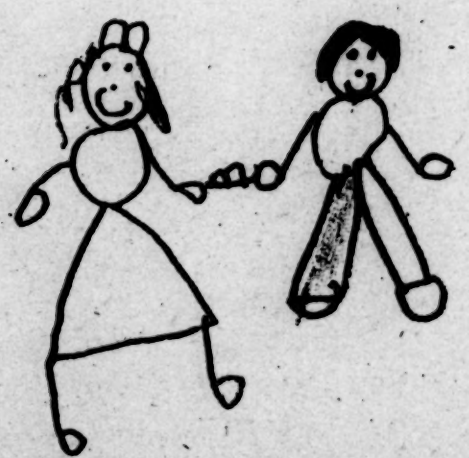
ROCHE

VI - PENTA

DROPS

TASTE

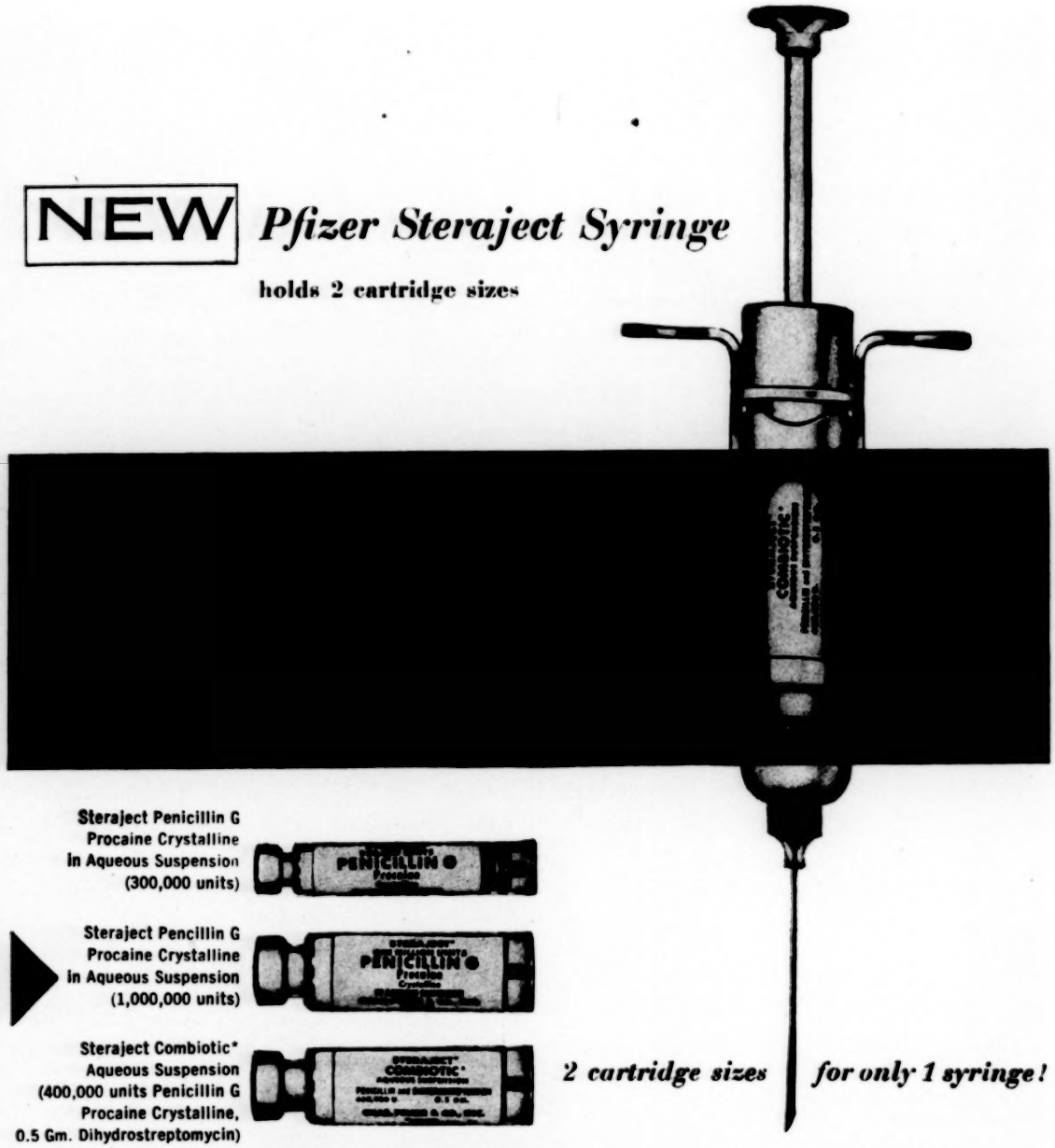
GOOD



Cholan

NEW *Pfizer Steraject Syringe*

holds 2 cartridge sizes



Steraject Penicillin G Procaine Crystalline in Aqueous Suspension (300,000 units)

Steraject Pencillin G Procaine Crystalline in Aqueous Suspension (1,000,000 units)

Steraject Combiotic* Aqueous Suspension (400,000 units Penicillin G Procaine Crystalline, 0.5 Gm. Dihydrostreptomycin)

Steraject Dihydrostreptomycin Sulfate Solution (1 gram)

Steraject Streptomycin Sulfate Solution (1 gram)

2 cartridge sizes | for only 1 syringe!

two cartridge sizes permit *full standard* antibiotic dosage

cartridges individually labeled

ready for immediate use

no reconstitution

for full details, ask your Pfizer Professional Service Representative

Steraject Cartridges:
each one supplied with sterile needle, foil-wrapped

introduced by [redacted] *world's largest producer of antibiotics*

*TRADEMARK, CHAS. PFIZER & CO., INC.

ANTIBIOTIC DIVISION • CHAS. PFIZER & CO., INC. • BROOKLYN 6, N. Y.

rapid response

new

non-hormonal

synthetic

"The latent period between the initiation of therapy and the appearance of appreciable benefit was short."[1]

BUTAZOLIDIN

(brand of phenylbutazone)

orally effective for relief of

ARTHRITIS *and allied disorders*

BUTAZOLIDIN brings quick relief and, often, functional improvement, to the majority of patients with rheumatoid arthritis, osteoarthritis, spondylitis, gout, arthritis with psoriasis, peritendinitis, fibrositis, and other painful musculoskeletal disorders.[1-3]

BUTAZOLIDIN

- **Broad Therapeutic Spectrum**
- **Potent Therapeutic Effect**
- **Prompt Action**
- **Low Ratio of Serious Side Effects**
- **Oral Effectiveness**

BUTAZOLIDIN is well within the means of the average patient.

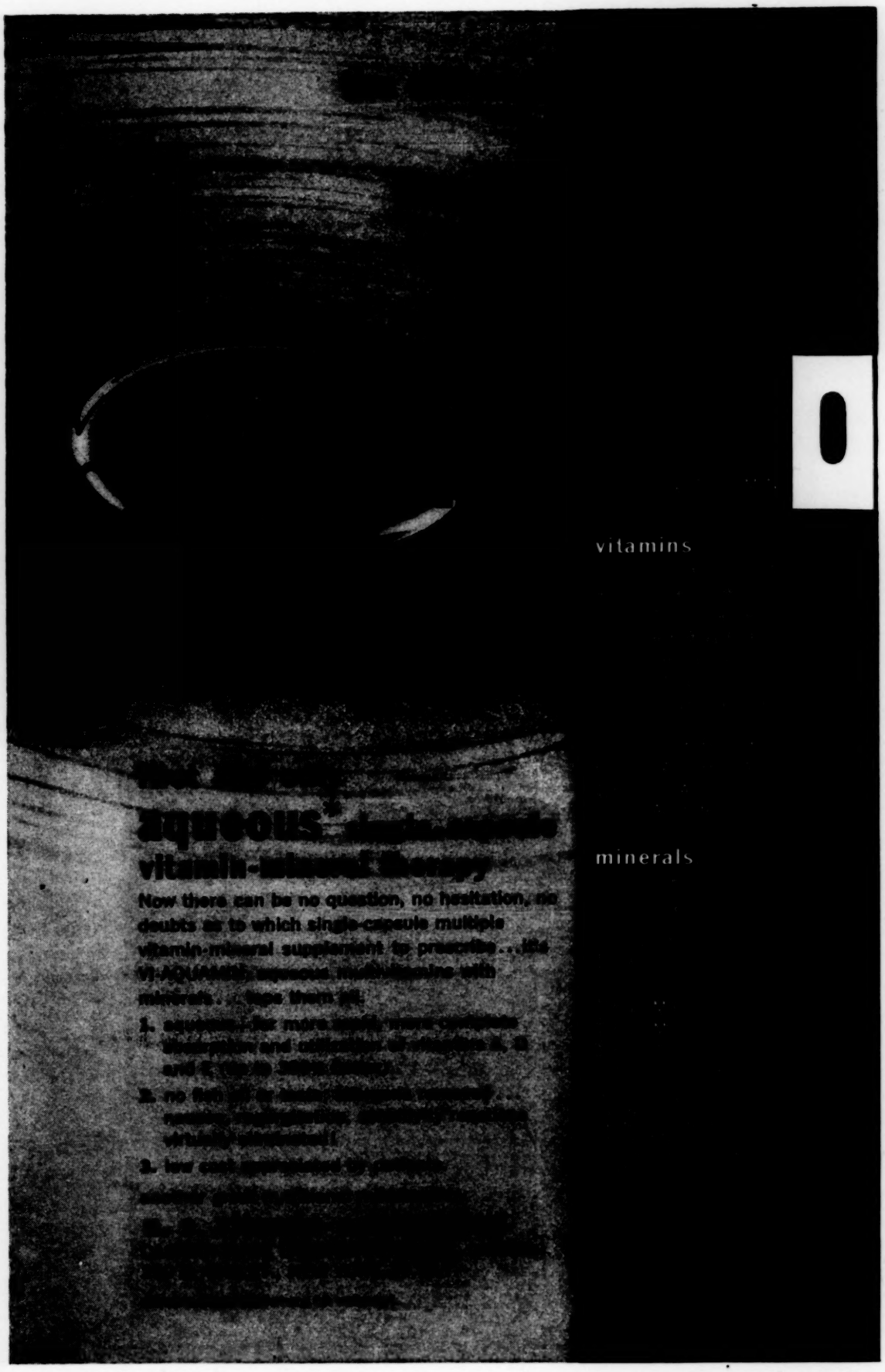
In order to obtain optimal results and to avoid untoward reaction it is highly desirable for the physician to become thoroughly acquainted with the characteristics of BUTAZOLIDIN before prescribing it. Physicians are urged to read the package circular carefully or to write for the BUTAZOLIDIN brochure, which will gladly be sent on request.

Availability: BUTAZOLIDIN® (brand of phenylbutazone) is issued in yellow-coated tablets of 200 mg. and in red-coated tablets of 100 mg.

1. Steinbrocker, O.; Berkowitz, S.; Ehrlich, M.; Elkind, M., and Carp, S.: Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, Ill., June 6, 1952.
2. Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952.
3. Smith, C. H., and Kuna, H. C.: J. M. Soc. New Jersey *49*:306, 1952.

Geigy

GEIGY PHARMACEUTICALS, *Division of Geigy Company, Inc.*
220 Church Street, New York 13, N. Y.


0
vitamins
minerals

ROUTINE THERAPY FOR INTERNAL HEMORRHOIDS

For the vast majority of cases of internal hemorrhoids requiring conservative treatment, the employment of RECTAL MEDICONE appears clearly indicated. The enormous prescription demand which this product enjoys, furnishes definite evidence of its value in this condition—particularly so when prompt symptomatic relief is vital for the comfort and well-being of the patient.

RECTAL MEDICONE

MEDICONE COMPANY • 225 VARICK STREET • NEW YORK 14, N. Y.

Massive Salicylate Dosage
without gastric disturbance?

yes! *with* Salcedrox®

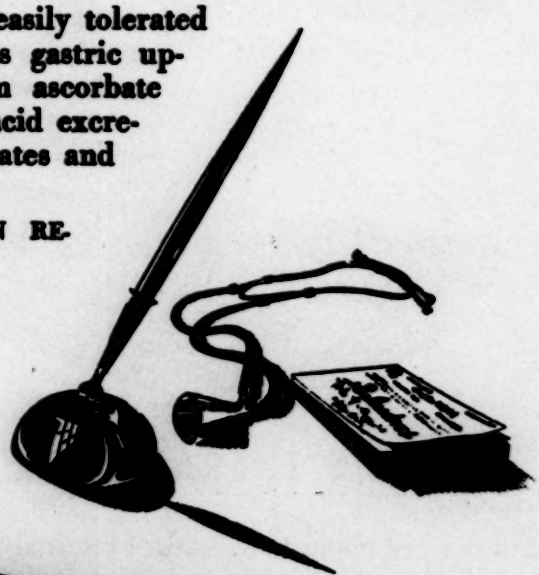
Salcedrox is highly useful whenever salicylates are indicated —in arthritis, rheumatoid involvements, neuromuscular pains and rheumatic fever.

The buffered sodium salicylate is more easily tolerated than salicylate alone—virtually abolishes gastric upset, even with massive dosage. Calcium ascorbate helps counteract the increased ascorbic acid excretion usually encountered in rheumatic states and in salicylate therapy.

PROFESSIONAL LITERATURE AVAILABLE ON REQUEST.

Each Salcedrox tablet contains:

Sodium Salicylate	5 gr. (0.3 Gm.)
Aluminum Hydroxide Gel, dried	2 gr. (0.12 Gm.)
Calcium Ascorbate	1 gr. (60 mg.) (equivalent to 50 mg. ascorbic acid)
Calcium Carbonate	1 gr. (60 mg.)



Salcedrox TABLETS

S. E. MASSENGILL BRISTOL, TENNESSEE

Successful Treatment of

NEURITIS WITH PROTAMIDE

(SHERMAN)

84 patients of 104 had complete relief of pain in sciatic, intercostal and facial neuritis with one daily injection of Protamide for five or ten days.

Smith reports "—49 were discharged as cured after five days of therapy."

No intolerance to Protamide, systemic or local was found in the 125 patients (104 plus 21 controls).

Two qualifications for practical application of this study are:

1 The elimination of cases due to mechanical pressure.

2 Early treatment after onset.

**Smith, Richard T: Treatment of Neuritis with Protamide. New York Medicine {Aug. 20} 1952.*

A card marked Neuritis will bring reprint and literature

SHERMAN LABORATORIES

IN PERSISTENT MALIGNANT HYPERTENSION

Here Is Immediate Relief of the Overwhelming Symptoms

SOLUTION INTRAVENOUS

VERILOID®

For the patient with markedly elevated systolic and diastolic blood pressures exhibiting such distressing symptoms as headache, disorientation, blurred vision and muscle twitching, here is a rapid, dependable means of providing relief.

Infused slowly by vein, Solution Intravenous Veriloid is capable of dropping both the systolic and diastolic pressures by as much as 30 per cent within a matter of minutes. This drop in tension is constantly under the control of the clinician, both in extent and duration of action. Coincidentally with the reduction in arterial pressure, profound subjective improvement is noted. After this improved circulatory state is maintained by Solution Intravenous Veriloid for a prolonged period, the blood pressure can be controlled subsequently by the administration of suitable oral medication.

Solution Intravenous Veriloid, generically designated alkavervir, is a purified ester alkaloidal fraction of Veratrum viride, biologically standardized for hypotensive potency in dogs. It has produced outstanding results in malignant hypertension, hypertensive crises (encephalopathy), and hypertensive states accompanying cerebral vascular disease.

Literature describing dosage and administration of Solution Intravenous Veriloid accompanies each package of the product and should be carefully read before administration is undertaken.

Solution Intravenous Veriloid is supplied in 5 cc. ampules.

ACCEPTED
AMERICAN MEDICAL ASSOCIATION

RIKER LABORATORIES, INC.

8480 Beverly Boulevard • Los Angeles 48, California

FOR THE ULCER PATIENT

IN SEARCH OF THESE

"FOUR FREEDOMS"

AIN

ptly relieves the

ic ulcer.

FROM GASTRIC

raises the

and maintai

secretion

in elec

rebound

disturbance

3 FREED

soothing, protective,

the gastro-duodenal

4 F

disintegrate

a pleasan

TABLETS

Robins

KEEPING PACE WITH TOMORROW

We are proud of our more than seventy years in the field of ethical pharmaceutical manufacturing — proud that they represent a time-tested reputation for pharmaceuticals of proven therapeutic value. • We are young in the strength of our determination to preserve that reputation and to keep pace—through research and the development of new and better products — with the needs of men of medicine who keep pace with tomorrow.

Robins

A. H. ROBINS COMPANY, INC.

RICHMOND 20, VIRGINIA

Ethical Pharmaceuticals of Merit since 1878

Wyeth®

1348 CASES

ONLY 4 PENICILLIN REACTIONS

WHY?

(only 3/10 of 1% in contrast to 5% for ordinary penicillin)

● Clinicians the world over have noted, not only the effectiveness, but also the rarity and mildness of reactions to BICILLIN—the new penicillin compound.

Thus, in 1348 cases, injected with single doses of from 300,000 to 2,500,000 units BICILLIN, only 0.3% developed penicillin reactions—pruritic dermatitis medicamentosa. In these few cases, this did not appear until 10 days after injection, and it cleared after 2 days in spite of persisting deposit of BICILLIN in the tissues.

Remember that the average rate of reactions to ordinary penicillin is approximately 5%.

INJECTION

BICILLIN* L-A

BENZETHACIL

DIBENZYLETHYLENEDIAMINE DIPENICILLIN G

penicillin blood levels for 2 weeks with single injection, 600,000 units

*Trademark

Question:

WHAT MAKES Biphetacel SUPERIOR?

Answer:

THE *EXCLUSIVE* 1:3 L/D RATIO!

"IN CURBING APPETITE and causing weight loss, a combination of Monobasic amphetamine phosphate containing a ratio of 1:3 of levo to dextro amphetamine (as found exclusively in Biphetacel) is more effective than the same amount of amphetamine contained in the racemic form where the ratio is 1:1 l/d . . ."*

Because of its exclusive 1:3 l/d ratio, Biphetacel curbs appetite more effectively, without nausea or nervousness, in both vagotonic or "sluggish" and sympathicotonic or "high strung" patients. In addition, it preserves an "enough-to-eat" feeling by decreasing gastric motility and prolonging emptying time of stomach, and assures normal elimination by supplying evenly distributed, non-nutritive, "no clump" bulk. Small dosage means low treatment cost.

Each Biphetacel tablet contains the preferred 1:3 l/d ratio as provided by Racemic Amphetamine Phosphate Monobasic 5 mg. and Dextro Amphetamine Phosphate Monobasic 5 mg.; Metropine® (methyl atropine nitrate, Strasenburgh) 1 mg., Sodium Carboxymethylcellulose 200 mg.

Dosage: 1 tablet ½ hour before meals, three times daily, for the vagotonic type. Increase this dose, if necessary, to achieve the desired clinical results. ½ tablet ½ hour before meals, three times daily, for one week for the sympathicotonic type. If no signs of intolerance develop, increase to 1 tablet. Supplied in bottles of 100 and 1000 scored tablets.

For literature and supply for initiating treatment, write Medical Service Department, R. J. Strasenburgh Co., Rochester 14, N. Y.

*Freed, S. C. and Mixel, M.—*in press*

PATIENTS RETAIN THEIR ZEST FOR FOOD . . . BUT THEY *"Eat Less and Like It!"*

Strasenburgh

FOUNDED IN 1886

A NEW REPOSITORY ACTHAR

To greatly expand the usefulness of ACTH in your practice

Administered As Easy As Insulin: HP*ACTHAR *Gel* can be injected subcutaneously as well as intramuscularly with a minimum of discomfort.

Fewer Injections: One to two doses per week may suffice in many cases (see package insert for complete dosage schedule or write for full information).

Rapid Response, Prolonged Effect: HP*ACTHAR *Gel* combines the two-fold advantage of sustained action over prolonged periods of time with the quick response of lyophilized ACTHAR.

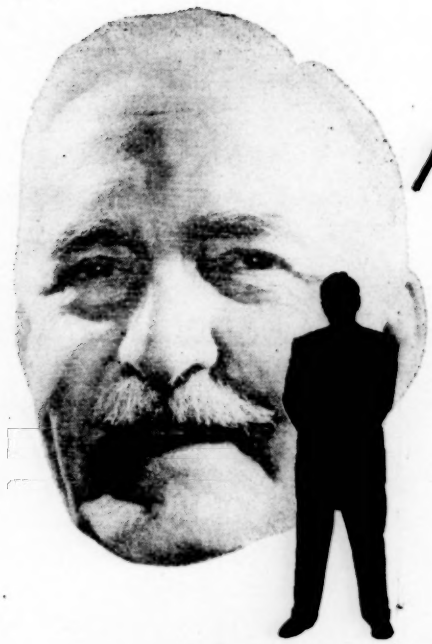
Much Lower Cost: Recent significant reduction in price, together with the reduced frequency of injections, have advanced the economy of ACTH treatment so markedly that it is now within everybody's reach.

Gel

*Highly Purified. ACTHAR® is the Armour Laboratories Brand of Adrenocorticotropic Hormone—ACTH (Corticotropin)

THE ARMOUR LABORATORIES
CHICAGO 11, ILLINOIS
world-wide dependability

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH



prescribed for a lifetime...

NEOHYDRIN*

THE DIURETIC TABLETS THAT WORK LIKE AN INJECTION

lifetime therapy—

NEOHYDRIN helps keep the cardiac patient in fluid and electrolyte balance for his lifetime—a lifetime that might be impossible without such control of water and salt metabolism.

day in, day out diuresis—

NEOHYDRIN daily, maintains a steady, uninterrupted diuresis. This allows more liberal salt intake which benefits the patient psychologically. Even more important, liberalized salt intake permits the daily physiologic intake and output of sodium required by the body and safeguards against salt depletion.

how to use this new drug

Maintenance of the edema-free state has been accomplished with as little as one NEOHYDRIN Tablet a day. Often this dosage of NEOHYDRIN will obtain per week an effect comparable to a weekly injection of MERCUHYDRIN.® When more intensive therapy is required one tablet or more three times daily may be prescribed as determined by the physician.

Gradual attainment of the ultimate maintenance dosage is recommended to preclude gastrointestinal upset which may occur in occasional patients with immediate high dosage. Though sustained, the onset of NEOHYDRIN diuresis is gradual. Injections of MERCUHYDRIN will be initially necessary in acute severe decompensation.

Contraindicated in acute nephritis and nephrosclerosis.

Any patient receiving a diuretic should ingest daily a glass of orange juice or other supplementary source of potassium.

prescribe NEOHYDRIN when indicated in

congestive heart failure • recurring edema and ascites • cardiac asthma • hypertensive heart disease dyspnea of cardiac origin • arteriosclerotic heart disease • fluid retention masked by obesity • and, for patients averse to their low-salt diet.

packaging **Bottles of 50 tablets. There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.**

Leadership in diuretic research

M-6

*Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

*TRADEMARK APPLIED FOR

Depo

Depo

Depo

Depo

Depo

a product of **Upjohn**

for medicine ... produced with care ... designed for health

Estrogenic problems present many facets— all are amenable to treatment with...

BENZESTROL

2,4 di (p-hydroxyphenyl)-3-ethyl hexane

— the multi-faceted synthetic estrogen is:

CLINICALLY EFFECTIVE: Prolonged beneficial effects are obtainable with BENZESTROL. BENZESTROL is effective orally, whereas natural estrogens lose a large proportion of activity when administered by mouth.

CLINICALLY ECONOMICAL: Therapeutically comparable doses of BENZESTROL are much less expensive than natural estrogens.

NON-TOXIC: Clinical studies have proved that BENZESTROL when administered in therapeutically effective doses, is singularly free from undesirable, toxic, side reactions[1-2] . . . as exhibited with some other synthetics.

supplied

ORAL — TABLETS
0.5 mg. (white) 100's and 1,000's
1.0 mg. (gray) 100's and 1,000's
2.0 mg. (orange) 50's, 100's & 1,000's
5.0 mg. (pink) 50's, 100's & 1,000's

TABLETS w/ *Phenobarbital** (yellow)
1 mg. Benzestrol with 15 mg. (¼ gr.) phenobarbital 100's

ELIXIR
15 mg. per fl. oz. Pint bottles

INTRAMUSCULAR
SOLUTION in OIL
5 mg. per cc. 10 cc. vials

AQUEOUS SUSPENSION
(Contains 2% benzyl alcohol)
5 mg. per cc. 10 cc. vials

LOCAL —VAGINAL TABLETS
0.5 mg. 100's

*Other pot cosmetic accepted.

AVERAGE DOSE: Menopause — 2 to 3 mg. daily, orally; or ½ to 1 cc. parenterally, every 3 to 5 days.

Control of Breast engorgement—5 mg. orally, 3 or 4 times for 5 to 6 days. Generous 2 mg. oral professional samples and complete literature on request.

References: 1. Holford, A.R.: J.A.M.A. 122:229 (1943)
2. Tallman, M.R.: Amer. Jnl. Obst. & Gyn. 46:345 (1943)

Schieffelin & Co. / Since 1794
Pharmaceutical and Research Laboratories
10 Cooper Square, New York 3, N. Y.

'POLYSPORIN'

ANTI-GRAM-POSITIVE

BROAD SPECTRUM

ANTI-GRAM-NEGATIVE

'POLYSPORIN' OINTMENT

INDICATIONS

- infected wounds resulting from trauma or surgery
- infected burns
- infected skin grafts
- abscesses and ulcers in any accessible location
- furuncles
- pyoderma
- ecthyma
- folliculitis
- infectious eczematoid dermatitis
- impetigo
- acne
- styes
- external ear infections
- eye infections such as:
  - conjunctivitis
  - blepharoconjunctivitis
  - scleritis
  - keratitis
  - dacryocystitis, etc.

SECONDARY INFECTIONS

superimposed on any dermatological condition

AVAILABLE IN

tubes of 15 Gm. with applicator tip

tubes of 1/8 oz. with ophthalmic tip

complete information will be sent on request

WHEN DIETARY SUPPLEMENTATION IS NEEDED...

what more could a supplement provide?

If the concept of an ideal dietary supplement could be formulated, it might well be one that provides qualitatively every substance of moment in human nutrition. It would provide those for which human daily needs are established as well as others which are considered of value, though their roles and quantitative requirements remain unknown.

How Ovaltine in milk approaches this concept, and how well the recommended three glassfuls daily augment the nutritional intake, is shown in the appended table. The two forms of Ovaltine available—plain and chocolate flavored—are closely alike in their nutrient values.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three Servings of Ovaltine in Milk Recommended for Daily Use Provide the Following Amounts of Nutrients

(Each serving made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk)

MINERALS		VITAMINS	
*CALCIUM	1.12 Gm.	*ASCORBIC ACID	37 mg.
CHLORINE	900 mg.	BIOTIN	0.03 mg.
COBALT	0.006 mg.	CHOLINE	200 mg.
*COPPER	0.7 mg.	FOLIC ACID	0.05 mg.
FLUORINE	3.0 mg.	*NIACIN	6.7 mg.
*IODINE	0.7 mg.	PANTOTHENIC ACID	3.0 mg.
*IRON	12 mg.	PYRIDOXINE	0.6 mg.
MAGNESIUM	120 mg.	*RIBOFLAVIN	2.0 mg.
MANGANESE	0.4 mg.	*THIAMINE	1.2 mg.
*PHOSPHORUS	940 mg.	*VITAMIN A	3200 I.U.
POTASSIUM	1300 mg.	VITAMIN B_{12}	0.005 mg.
SODIUM	560 mg.	*VITAMIN D	420 I.U
ZINC	2.6 mg.		

*PROTEIN (biologically complete)	32 Gm.
*CARBOHYDRATE	65 Gm.
*FAT	30 Gm.

*Nutrients for which daily dietary allowances are recommended by the National Research Council.

oral penicillin t.i.d.

. . . for the more common bacterial infectious diseases

Just 1 or 2 Pentids Tablets t.i.d. are particularly effective . . . convenient, easy-to-take . . . cause fewer side effects . . . and are less than ½ the cost of the newer antibiotics.

Bottles of 12 and 100.

formulated for convenient t.i.d. dosage **Pentids**

Squibb 200,000 Unit Penicillin Tablets

"PENTIDS" IS A TRADEMARK OF E. R. SQUIBB & SONS

SQUIBB

ganglionic block in hypertension

to reduce blood pressure and relieve symptoms—a new, potent oral hypotensive

Extensive clinical use has demonstrated Methium's ability to

1. reduce blood pressure to more normal levels
2. relieve hypertensive symptoms
3. provide symptomatic relief in some cases even where pressure cannot be lowered.

An autonomic ganglionic blocking agent, Methium *(hexamethonium chloride)* inhibits nerve impulses that produce vasoconstriction—thereby causing blood pressure to fall.

In successfully treated patients, receding pressure is accompanied by relief of headache, dizziness, palpitation and fatigue. In other cases, where blood pressure does not respond to therapy, symptomatic improvement may nonetheless be noted.

Methium is a potent drug and should be used with great caution when complications exist —impaired renal function, coronary artery disease and existing or threatened cerebral vascular accidents. Complete instructions for prescribing Methium are available on written request or from your Chilcott detail man and should be consulted before using the drug.

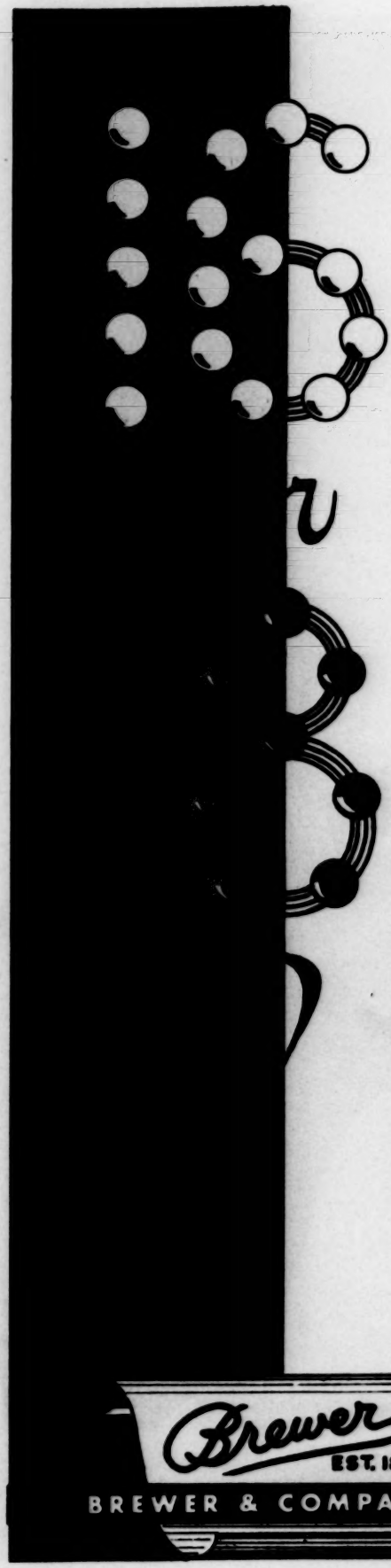
Methium is supplied in both 125 mg. and 250 mg. scored tablets in bottles of 100 and 500.

Methium® CHLORIDE

(BRAND OF HEXAMETHONIUM CHLORIDE)

CHILCOTT *Laboratories* INC. MORRIS PLAINS, NEW JERSEY

FORMERLY THE HALTINE COMPANY



Which

WOULD YOUR PATIENT PREFER?

Many patients who take oral diuretics rebel at the number of tablets which they are forced to take daily (the average oral dose of ammonium chloride is 4 to 8 Gm. daily). In order to facilitate taking of sufficient ammonium chloride for effective diuresis, we have enteric coated a 1 Gm. tablet of this substance.

●

AMCHLOR

IMPROVED AMMONIUM CHLORIDE

Recent clinical papers have shown that sufficient dosage of ammonium chloride, besides being an effective diuretic, is of value in Meniere's disease, premenstrual tension, and aids to eliminate nausea occurring in stilbestrol therapy. The next time you prescribe an oral diuretic, prescribe AMCHLOR. . . .

ONE GRAM TABLET—
ENTERIC COATED

For samples just send your Rx blank marked **13AM12**

Brewer
EST. 1852

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

ONE KILLS FASTER

Antiseptics that stab at bacterial invasions ...killing some but not all organisms... lack decisive germicidal action.

Zephiran chloride—a bacteri*cidal* agent—kills hemolytic streptococcus, staphylococcus, Escherichia coli as well as many other pathogens completely within seconds or a few minutes in vitro. A *refined* antiseptic, pharmacologic tests for tissue tolerance are made on each lot of Zephiran chloride.

Supplied as:

Aqueous Solution 1:1000, bottles of 8 oz. and 1 U. S. gallon.

Tincture 1:1000, tinted and stainless, bottles of 8 oz. and 1 U. S. gallon.

Concentrated Aqueous Solution 12.8%, bottles of 4 oz. and 1 U. S. gallon (1 oz.=1 U. S. gallon 1:1000 solution). Must be diluted.

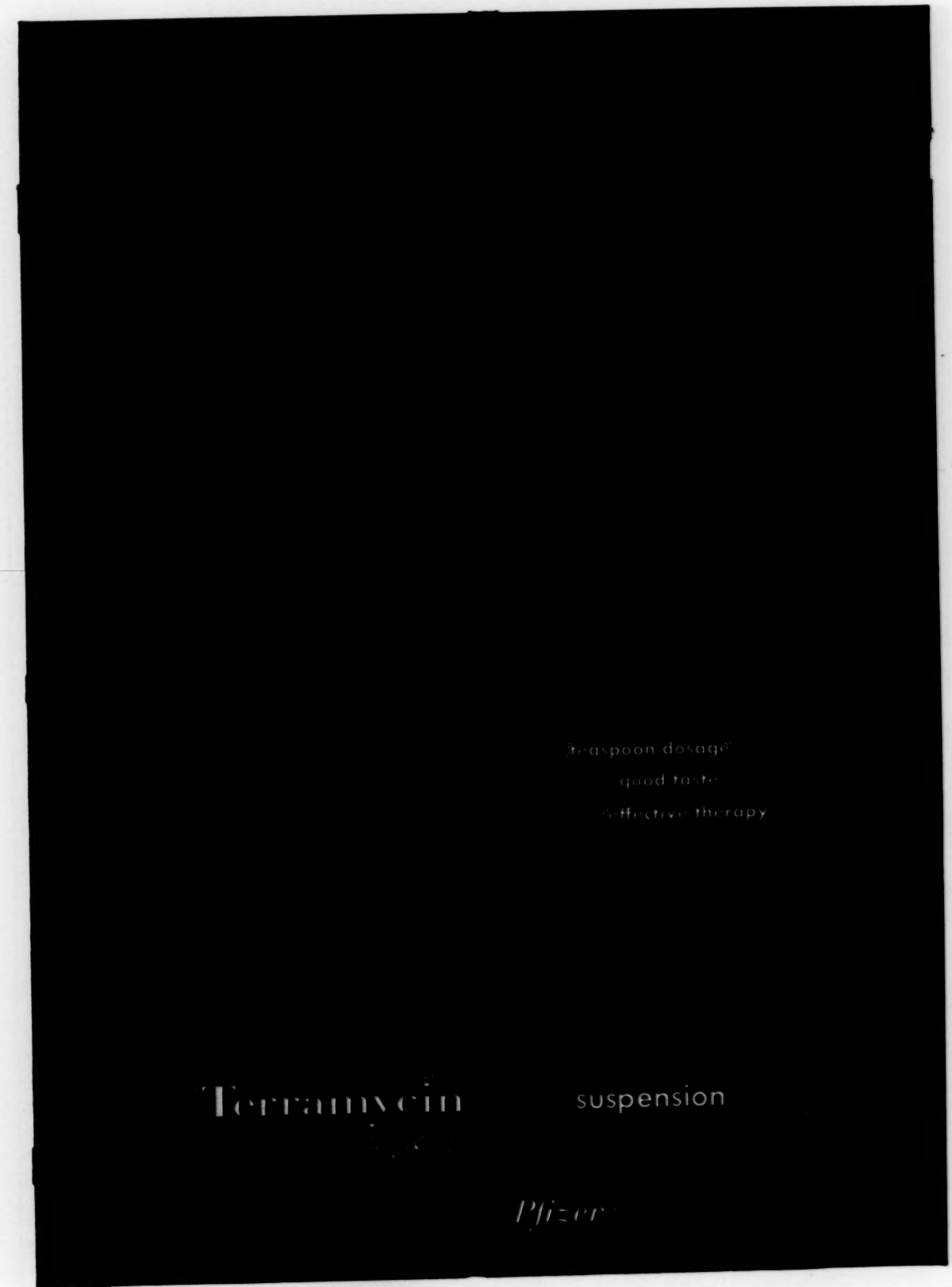
ZEPHIRAN®
CHLORIDE

for antisepsis with finesse...

Winthrop-Stearns Inc.

New York 18, N. Y. • Windsor, Ont.

Zephiran, trademark reg. U.S. & Canada, brand of benzalkonium chloride refined



DON'T MISS APPEARING REGULARLY IN THE J. A. M. A.

FOR

Christmas . THE IDEAL GIFT FOR

YOUR COLLEAGUE OR DOCTOR FRIEND

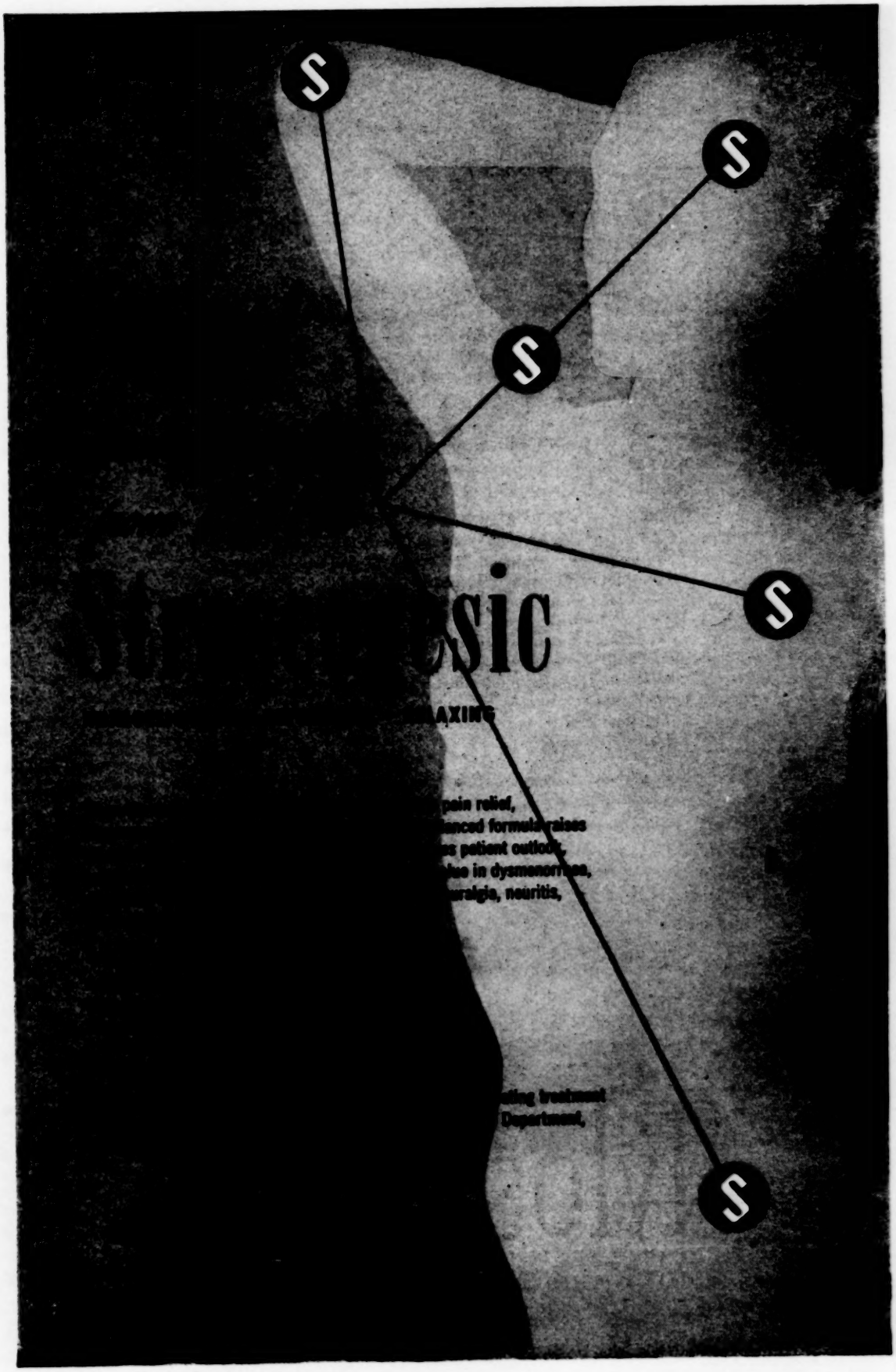
An up-to-date medical journal any doctor will take pride in having in his library—beautifully printed and illustrated—a publication that will provide both pleasure and inspiration.

The American Journal of Medicine

49 West 45th St. New York 36

Yearly Subscription $12.00 U.S.A.

Canada and Pan-American Union $13.00 Foreign $15.00


S
S
S
S
S
sic
AXING
pain relief,
anced formula raises
s patient outlook,
ue in dysmenorrhea,
uralgia, neuritis,
ating treatment
Department,

Prejudice-Free Study Points the Way to Greater Comfort for the Menopausal Patient

Three groups of investigators were supplied with preparations labeled only by number. Although identical in appearance, the tablets had the following compositions:

AE-1—Diethylstilbestrol, 0.25 mg.
AE-2—Diethylstilbestrol, 0.25 mg., plus methyltestosterone, 5 mg.
AE-3—Methyltestosterone, 5 mg.
AE-4—Placebo

Investigators were told which was the placebo, but identities of the first three were not disclosed until the studies and reports had been completed. Thus, there could be no possible bias on the part of either physician or patient.

Clinicians found that the addition of androgen to estrogen (1) often affords an increased feeling of well-being, (2) tends to avert mild but unpleasant side-effects such as breast turgidity and pelvic congestion, and (3) usually prevents the complication of uterine bleeding. *Preference for AE-2 ('Tylosterone') was expressed by two-thirds of the patients.*

Full details of these studies are available. May we send you literature or samples?

Eli Lilly and Company • Indianapolis 6, Indiana, U.S.A.

Lilly

Helps avert side-effects of estrogen therapy

TABLETS

'Tylosterone'

(DIETHYLSTILBESTROL AND METHYLTESTOSTERONE, LILLY)

The American Journal of Medicine

Vol. XIII DECEMBER, 1952 No. 6

Editorial

The Basis for Dietary Treatment in the Prevention and Control of Atherosclerosis

MAN is unique among mammals in his predisposition to atherosclerosis. In this country and in western Europe the disease is so prevalent that half of the population may be significantly affected before attaining the age of fifty.[1] It is now the leading cause of death and is responsible for untold physical and mental disability. Recital of its consequences in the press and in the literature of insurance companies and other organizations has excited among the laity a fear not unlike that formerly reserved for cancer, and also a demand that physicians apply immediately the results of investigation in its prevention and control. Expediency, if no other consideration, demands application of what is known but with avoidance of measures which are scientifically unsound or unnecessarily frustrating and restrictive.

Prominent among the suggestions concerning the nature and control of atherosclerosis is the proposal that the condition arises because of an ill chosen or excessive intake of lipids in the food and that its development and consequences can be delayed or escaped by selection or adjustment of the intake of cholesterol or fat. The idea derives some indirect support from laboratory investigations which have shown that atheromatous patches have a lipid composition initially quite like that of the plasma, that their formation is accelerated in clinical conditions which are characterized by hypercholesterolemia and that the ingestion of very large amounts of cholesterol by animals not naturally afflicted with the disease produces in normal intact arteries lipid deposits not unlike those seen in human atherosclerosis. More detailed studies of actual cases of advanced human atherosclerosis have disclosed deviations from normal standards in cholesterol concentration, cholesterol-phospholipid ratios and the distribution of lipoproteins, but have failed to reveal any constant or invariable chemical characteristic of the condition. Taken as a whole, however, the experimental observations leave little doubt that there is in man some defect in lipid metabolism which contributes to the abnormal deposit in blood vessels. Nevertheless, it must be admitted that nothing in the basic studies has directly incriminated the dietary and that trials of various modifications of lipid intake for the present are to be regarded as entirely empiric.

Their scientific evaluation offers peculiar difficulties. The high incidence of atherosclerosis, its chronicity and highly variable course and the absence of any adequate clinical criteria for estimating its extent and anatomic distribution are some of the factors which render the establishment of adequate controls almost impossible. Furthermore, the objectives of the treatment are various. Ideally the diet should limit or prevent the deposit of lipids in the arterial walls or, even more hopefully, should reverse the process and cause disappearance of lesions already formed. The plaques, however, represent only one of the serious aspects of the condition. While their presence may grossly limit the caliber of vessels to the extent of precarious circulation of important organs, they do not in themselves constitute the most frequent cause of death or disabling illness. Of great importance is the control of hypertension which not only accelerates the rate of deposit of lipid but also favors the rupture of vessels weakened by atheromatous patches. Most desirable of all therapeutic aims is the inhibition or prevention of clotting which is probably

[1] WILENS, S. L. Bearing of general nutritional state on atherosclerosis. *Arch. Int. Med.*, 79: 129, 1947.

responsible for most of the fatalities and more serious complications.

Criteria for estimation of the degree to which all or any of these results can be achieved by treatment are so primitive and faulty that final conclusions concerning the benefits of diet must depend upon statistical analyses or the development of more precise tests. In the meantime scrutiny of what is already known may be useful in determining the justification and direction of further dietary trials.

Two types of diet are now in frequent use. One attempts avoidance of cholesterol with or without strict limitation of fat intake. The other emphasizes a goal of limited fat ingestion with avoidance of surfeit and obesity, but without great emphasis upon the amount of cholesterol in the food.

Cholesterol-free diets can be given with adequate or even high caloric intake, since simple carbohydrates and vegetable fats contain no cholesterol. However, because they require complete abstinence from eggs, milk and many other food staples, they are unpalatable and extremely difficult to maintain. To the patient they represent hardship, which can be tolerated over long periods only by the promise or demonstration of outstanding practical advantages.

Some careful observations have been made on the effects of varying the amount of cholesterol in the diet. It is known, for instance, that complete avoidance of cholesterol does not materially change the concentration of cholesterol in the serum. Furthermore, single ingestion of very large amounts of cholesterol exerts surprisingly little influence upon serum cholesterol levels. When, however, a diet containing no cholesterol is combined with a very low fat intake, the level of serum cholesterol is significantly reduced.[2] Gofman's observations have indicated also that a diet with similar although less extreme restrictions may lower the level of the S_f10–20 bodies to which he attributes importance in the pathogenesis of atherosclerosis.[3] It is significant, however, that when vegetable fat but no cholesterol is added to such diets, the cholesterol concentration in the blood returns promptly to predietary levels.[4]

At present it is upon such observations as these that the scientific basis for a cholesterol-free diet must rest. Obviously they do not prove the efficacy of restricting cholesterol alone. They provide no data to indicate that the avoidance influences the development of atherosclerosis, that it lowers hypertension or that it inhibits the tendency to intraluminal clotting. This conclusion, while disappointing to those who have placed their hopes on the therapeutic use of a cholesterol-free diet, is not unexpected by others who have investigated more completely the details of cholesterol metabolism. Studies with isotopes have shown that cholesterol may be synthesized by cells of many organs and tissues in daily amounts greatly in excess of those ingested in any customary diet and more than sufficient to maintain usual cholesterol concentrations in the serum even when no cholesterol is ingested.[5]

While the experiments have thus far failed to establish proof of benefit from a diet whose only merit is complete exclusion of cholesterol, they have strongly indicated that restriction of fats might be helpful. Judgment concerning the efficacy of low calory, and hence low fat, diets must at the moment depend less upon controlled experiments and chemical evidence than upon clinical and statistical data.

Physicians through many generations have held persistently to the idea that gluttons have a relatively high morbidity and mortality from vascular disease. Greater average longevity and relative freedom from vascular accidents have been repeatedly claimed for the spare and the frugal. In recent years these long prevalent impressions have received abundant confirmation from the careful statistical analysis of insurance risks which have shown that the presence of obesity tends not only to shorten life but also predisposes to hypertension and relatively early death from cardiac disorders. The statistics of Wilens on the autopsy service at Bellevue Hospital[1] indicate that atheromatous plaques are more abundant and advanced in those who are overweight. Still more recent information indicates that overnutrition may have an influ-

---

[2] Keyes, A. The relation in man between cholesterol levels in the diet and in the blood. *Science*, 112: 79, 1950.

[3] Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B. and Nichols, A. V. Lipoproteins in atherosclerosis. *Am. J. Med.*, 11: 358, 1941.

[4] Hildreth, E. A., Mellinkoff, S. M., Blair, G. W. and Hildreth, D. M. The effect of vegetable fat ingestion on human serum cholesterol concentration. *Circulation*, 3: 641, 1951.

[5] Gould, G., Campbell, D. J., Taylor, C. B., Kelly, J. B., Jr., Warner, I. and David, C. B. Origin of plasma cholesterol using carbon^{14}: *Fed. Proc.*, 10: 191, 1951.

ence upon the occurrence of intraluminal clotting.

Dedichen[6] has reviewed the mortality statistics from circulatory disease in Oslo for the years 1940 to 1945, a time when dietary restrictions were rigidly enforced, and has compared them with those before and after the period of diminished food intake. He noted a sharp reduction in mortality which began within a few weeks of the institution of deprivation, reached its lowest point in about three years, and continued with little change until a normal dietary had been restored. Within a short time following the removal of restrictions the death rate rose again to its pre-deprivation level. Possibly even more impressive was the observation of a similar decline in the incidence of thromboembolic phenomena following surgery. While the change in death rate from circulatory disease might conceivably be explained by an effect upon the atheroma of vessels, the incidence of thrombosis of veins could not be so attributed. The most obvious inference to be drawn from the Norwegian statistics is that a low calory, low fat diet may diminish the tendency to thrombosis, and that surfeit may increase it.

Thus present information, although incomplete and in large part inferential, indicates that overnutrition shortens life, predisposes to hypertension, increases the extent of atheromatous plaque formation, and possibly increases the tendency to intraluminal thrombosis. It would appear therefore that during the period while further scientific analyses of diet are being attempted, a low fat, low calory diet may be advised with the expectation of partial protection against the rapid development and the complications of atherosclerosis. Since Man is an atherosclerotic animal and since the disease probably affects to some degree most individuals in middle and later life, the advice should not be limited to the obese or to those who have suffered obvious complications of atherosclerosis.

DAVID P. BARR, M.D.

---

[6] DEDICHEN, J., STROM, A., ADELSTEN, JENSEN, R. and CLOSS, K. Incidence of Atherosclerotic Disease during War Years, p. 117. Transactions of the Fifth Josiah Macy, Jr. Foundation Conference on Factors Regulating Blood Pressure. New York, 1951. Corlies Macy & Co.

Clinical Studies

Quantitative Studies of Ascitic Fluid Circulation with Tritium-labeled Water*

THEODORE C. PRENTICE, M.D., WILLIAM SIRI *and* ETHEL E. JOINER
Berkeley, California

WITH the introduction and utilization of tracer methodology in recent years has come an increasing realization of the dynamic status of most body constituents. The present investigation extends this concept to the problem of ascites formation and introduces a method for measuring the volume of ascitic fluid and quantitating the inflow and exit of water from the peritoneal cavity per unit time.

Most of the current literature concerning the problem of ascites formation centers about the concept that ascitic fluid is a more or less static reservoir of fluid.[1,2] The fluid has been regarded as accumulating and being trapped in the peritoneal cavity due to a combination of factors. These include the opposing forces, as originally proposed by Starling,[3] of (1) increased portal venous pressure minus ascitic hydrostatic pressure, or net hydrostatic pressure acting to increase the ascitic fluid volume and (2) plasma colloid-osmotic pressure minus ascitic colloid-osmotic pressure, or net colloid-osmotic pressure acting to reabsorb ascitic fluid into the vascular system. Typically, factor (1) is increased due to portal hypertension and (2) is decreased because of hypoalbuminemia and increased protein content of ascitic fluid.

More recent developments have been the demonstration of (3) marked renal retention of sodium[4,5] and (4) increased amounts of circulating antidiuretic hormone in patients with portal cirrhosis.[6] Changes in permeability of portal capillary membranes have been postulated but not proven.[7] The interrelationship of these factors and their exact association with ascites formation remains unexplained.

This study demonstrates that ascitic fluid is by no means a trapped or segregated reservoir of fluid. Rather, it is a continuously circulating pool, 40 to 80 per cent of which enters or leaves the peritoneal cavity each hour. An attempt is also made to clarify further the interrelationship of the mechanisms which are responsible for ascites formation.

MATERIALS AND METHODS

Six patients with ascites were studied. Four had classical Laennec's cirrhosis and two were diagnosed as metastatic peritoneal carcinomatosis. Data concerning each patient are summarized in Table I.

Each patient was given 2 mc. of tritium-labeled water either intravenously or into the ascitic fluid. Serial samples of ascitic fluid during a period of seven to twenty-four hours immediately following injection were obtained using the following method: A site in the midline of the abdomen, midway between the symphysis and umbilicus, was selected. After the usual sterilization procedures were completed a No. 13 needle with a fitted trocar was inserted into the peritoneal cavity at this site, the trocar withdrawn and No. 18 polyethylene tubing threaded through the needle. The needle was then removed leaving the tubing in place. This tubing could be clamped with an ordinary small hemostat, which was taped to the abdominal wall, and samples obtained by simply opening the hemostat. Successive blood samples were taken by the routine venipuncture technic. They were heparinized, centrifuged and the plasma separated and stored in the refrigerator. Analysis for tritium content of ascites and plasma was carried out using methods developed in this laboratory.[8,9] The patients' red blood cells were labeled with P^{32} by the method of Hevesy and Zerahn[10] as modified in this laboratory.[11,12]

* From the Section on Experimental Medicine, Donner Laboratory, University of California, Berkeley, and Highland-Alameda County Hospital, Oakland, Calif. This work was supported by the Life Insurance Medical Research Fund and the U. S. Atomic Energy Commission.

One cc. of the labeled whole blood was then injected into the peritoneal cavity at the same time as the tritium solution. Mixing of the labeled cells in the ascitic fluid was hastened by vigorous shaking of the patient's abdomen and frequent change of position. A plateau level of radioactivity due to P^{32} in the ascitic fluid was noted after fifteen minutes indicating complete mixing of cells within the ascitic fluid. The plateau lasted a variable period of time (thirty minutes to three hours). This activity when compared with that of a standard determined the volume of ascites.

TABLE I

Patient	Age	Weight (lb.)	Total Body Water (L.)	Ascites (L.)	K_A Hours^{-1}	K_B Hours^{-1}	Rate of Transfer (L./hr.)	Diagnosis
1	48	142	35.8	5.3	.47	.08	2.47	Portal cirrhosis
2	51	170	50.6	6.6	.40	.06	2.64	Portal cirrhosis
3	60	140	40.0	14.8	.50	.30	7.45	Portal cirrhosis
4	70*	95	23.6	4.8	.61	.15	2.91	Peritoneal carcinomatosis
5	65*	187	48.2	8.0	.53	.11	4.26	Peritoneal carcinomatosis
6	39	149	43.0	4.7	.82	.10	3.80	Portal cirrhosis

* Represents female.

The values for the constants have been rounded off to two decimal places because of the limits of accuracy of their determination.

THEORY

If the tracer kinetics of a biologic system can be demonstrated to conform to a well defined model whose properties are precisely known, quantitative information concerning the system in question becomes available. It was found that the present biological system does conform to a closed, two-compartment model as illustrated in Figure 1. Two principal factors were important in the selection of the model. First, the change in quantity of tritium in either compartment is described by a single exponential function and, secondly, the concentration of tritium approaches a common level in both compartments.

In such a system (1) compartments A and B may be of differing size, (2) the total amount of material in the system remains essentially constant during the intervals considered here and (3) equal amounts of content are exchanged from one to the other per unit time.

Mathematically this steady state system can be described by the simple algebraic equations:

$$(1)\quad A + B = \text{constant}$$

where A = volume of ascites
B = volume of body water minus ascites

$$(2)\quad K_A A = K_B B$$

where K_A = fraction of ascites leaving peritoneal cavity per hour
K_B = fraction of body water minus ascites entering peritoneal cavity per hour

After injection into either compartment the movement of tracer, and therefore of water, into

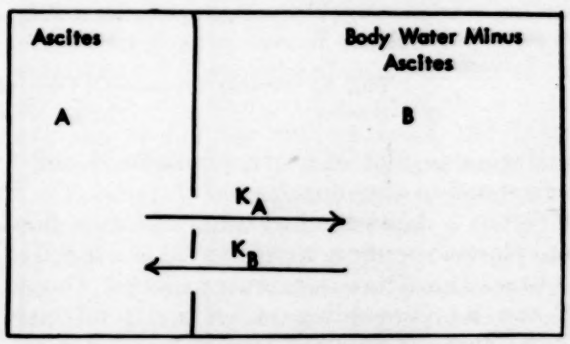


FIG. 1. Two compartment model.

and out of compartment A or B is described by differential equations (3) and (4), respectively.

$$(3)\quad \frac{dX}{dt} = -K_A X + K_B Y$$

where X = quantity of tracer in A
Y = quantity of tracer in B

$$(4)\quad \frac{dY}{dt} = -K_B Y + K_A X$$

When equilibrium of the tracer throughout body water has been reached

$$(5)\quad \frac{dX}{dt} = -K_A X + K_B Y = 0$$

$$(6)\quad \frac{dY}{dt} = -K_B Y + K_A X = 0$$

Since, assuming tritium to be a perfect tracer, the movement of tritium will be entirely analagous to that of water, equations 5 and 6 correspond to equation 2.

Figure 2 shows the logarithm of ascitic fluid and plasma specific activity plotted as a function of time. This figure represents patient 2. Curves A and B, representing ascites and total body water minus ascites, are seen to be asymptotic. The common asymptote of the two curves corresponds to uniform distribution of tritium throughout the total body water. The specific activity at the asymptotic value, when compared with the specific activity of a standard, determines the total body water. The rates at which Curves A and B approach one another are determined by (1) rapid exponential mixing of tritium within ascitic fluid, plasma, interstitial and intracellular fluid, with half-times of the order of five minutes to one-half hour. The present curves do not, and are not intended to, delineate accurately these fast-mixing components; (2) a slower exponential component with a half-time determined by the rate of water transfer into and out of the peritoneal cavity and the volumes of Compartments A and B.

When integrated for the case of injection into ascites (compartment A) equation 5 yields

$$(7)\quad X = \frac{X_0 K_B}{K_A + K_B}\left(1 + \frac{K_A}{K_B} e^{-(K_A+K_B)t}\right)$$

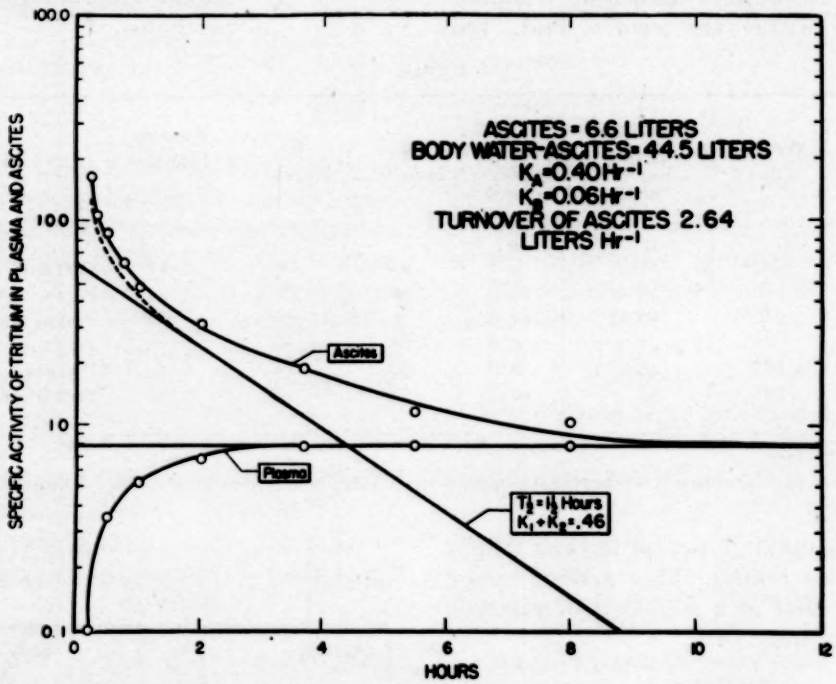


FIG. 2. Showing exponential rates of tritium transfer out of ascites and into plasma.

Likewise integration of equation 6 results in

$$(8)\quad Y = \frac{X_0 K_A}{K_A + K_B}\left(1 - e^{-(K_A+K_B)t}\right)$$

It should be noted that for intravenous injection (compartment B) the correct form of the equations will be found by exchanging X and Y and subscripts A and B in equations 7 and 8. The symbols retain their meaning as outlined for equations 5 and 6. X_0 refers to the quantity of tracer injected into the compartment.

It will be noted that in both instances the observed rate constant equals $(K_A + K_B)$ which is the slope of the slow component. Since the slope is determined by K_A *plus* K_B it will be the same for both compartments and will be the same whether tritium is injected into ascites or the circulation.

Curves A and B then are made up of a group of exponential components. The number of early, rapid components and their accurate

definition are not brought out by the present experimental data. The slowest component, however, is easily separated and clearly defined. Since the early components are not concerned with the turnover of ascites, the present discussion is based on the slow component. This component is not present in normal individuals but does appear in all the patients with ascites, none of whom had any edema. Therefore its identification with ascites appears fully justified. Moreover, the reasonable agreement between ascitic fluid volumes, as determined by extrapolation of this component, with values obtained by independent methods further establishes this identity.

Extrapolation of the slow component of Curve A to zero time permits calculation of the volume of ascites. Knowing the volume of ascites and total body water, the volume of Compartment B is now available by simply subtracting the volume of ascites from the total body water. Two equations in K_A and K_B are thus available:

(9) $K_A + K_B$ = slope of slow component as measured from experimental data

(10) $\frac{K_A}{K_B} = \frac{B}{A}$

We can therefore separate K_A and K_B, and K_AA will equal K_BB.

In one instance (case 4) the tritium was injected into compartment B (intravenously) rather than compartment A. Although $K_1 + K_2$ would be unaltered by such a change in procedure, the volume of ascites must be calculated by a different method. After the calculation of total body water, which is carried out as previously described, the slow component of curve B is extrapolated to zero time. The specific activity so obtained is added to the specific activity at equilibrium. The resulting value, when compared with the standard, determines the volume of body water minus ascites. Subtracting this volume from total body water yields the volume of ascites. The separation of K_1 and K_2 and the determination of the absolute rates of flow into and out of compartments A and B are then carried out as previously described.

It should be pointed out that when the tracer is injected into the ascitic fluid, all calculations can be carried out from the ascites curve. Plasma samples are required only to establish more firmly the common asymptote.

RESULTS

The experimental data as presented in Table 1 indicate that a large volume of water, varying from 40 to 80 per cent of the total ascitic fluid volume, enters and leaves the peritoneal cavity per hour. Thus a patient with a volume of ascites of 6 L., which is a common ascitic fluid volume, would be turning over approximately 58 to 115 L. of water per day in the peritoneal cavity. The volume of ascites will remain constant if inflow and outflow rate are equal. However, such a small discrepancy between inflow and outflow rate as 50 cc./hour, as compared with an average total transfer of 2 to 4 L./hour, would reduce or increase ascitic fluid by 1,200 cc. daily. It is apparent, then, that a very delicate balance must exist between rates of inflow and outflow to prevent large daily fluctuations in ascitic fluid volume.

The total volumes as determined by this method are an approximation rather than an accurate measure. In patients 4, 5 and 6 the total ascitic fluid volumes were checked by an independent method; one by the weight of the patient before and after paracentesis and the volume of fluid recovered, the latter two by the dilution of P^{32}-labeled red cells introduced into the peritoneal cavity. In all cases the volumes checked within less than a Liter, the largest difference being 0.9 L. and the smallest 0.1 L.

The single slow component in Curves A and B should be identical, as was stated earlier. In actuality it is found that although in some cases they agree closely, in others the slow component of curve B tends to have a slightly shorter half-time. We believe this is due to the inclusion of more rapid mixing components in total body water which, because of the present experimental error and limited number of points on the curve, we are unable to separate completely.

COMMENTS

McKee et al.[13] suggested the possibility that ascitic fluid might be a circulating medium. The demonstration of prompt removal of introduced fluid, plasma, and even red cells from the normal peritoneal cavity[14,15] plus the rapid exchange of C^{14}-labeled proteins between plasma and the ascitic pool in dogs with experimental ascites[16,17] was interpreted by these investigators as good evidence for simultaneous formation and reab-

sorption of ascitic fluid. The lymphatic apparatus in diaphragm and pelvis was regarded as the most likely site of reabsorption in these animals.

The present studies in humans provide definite evidence that rapid transfer of ascitic fluid takes place and quantitate the magnitude of this circulation. The opposing factors for production or reabsorption of ascitic fluid must be regarded, therefore, as functioning rapidly and simultaneously rather than acting to nullify one another. With the above observations in mind, further examination of the chain of events leading to ascites formation is possible. It is quite evident that the capacity for reabsorption of both solids and fluids from the normal peritoneal cavity is considerable. Furthermore, the present study would indicate that this function remains operative in patients with ascites formation due to portal cirrhosis and metastatic peritoneal carcinomatosis.

Ascites formation, no matter what the cause, is dependent upon an imbalance between inflow and outflow from the peritoneal cavity. Either an excess of inflow or a deficit in outflow could be the responsible factor. Here, however, it becomes necessary to consider the concept of a maximum reabsorption capacity. A patient, for example, with Laennec's cirrhosis could develop considerable portal hypertension, with transudation of large amounts of fluid into the peritoneal cavity. Until the maximum reabsorption capacity, or ascites threshold, is exceeded however, reabsorption will keep pace with transudation and ascites will not develop. If other factors such as sodium and water retention, which could further increase the inflow load, or hypoproteinemia which will decrease the reabsorptive capacity, then supervene, ascites may result. It is not too surprising, therefore, that certain patients with marked obstruction of the portal venous system do not develop ascites or that some patients with considerable hypoproteinemia likewise remain free of ascites. They simply have not reached the point where, either because of increased inflow or decreased outflow, fluid enters the peritoneal cavity faster than it leaves.

Likewise, the variation in response to dietary sodium restriction, the elevation of serum proteins by various means and the other usual therapeutic measures are understandable. One patient with a high degree of portal obstruction may produce ascitic fluid faster than it can be reabsorbed even when serum protein concentration has reached normal levels whereas in another patient with less obstruction or less sodium and water retention such a therapeutic measure will be successful. Thus many combinations and gradations of the factors leading to ascites formation are possible and a quantitative estimate of *each* factor must be at hand before the response to therapy becomes predictable.

The physiologic mechanism for rapid reabsorption of water from the peritoneal cavity in the presence of increased portal pressure and decreased effective plasma colloid osmotic pressure remains unexplained. Volwiler et al.[18] have demonstrated total hepatic lymph flows of 2 to 6 L. daily in 16 kg. dogs with experimental ascites. On a weight basis this would correspond to 9 to 26 L. in 70 kg. humans. However, their experimental method, constriction of the thoracic portion of the inferior vena cava or the hepatic vein, is open to question as to its relevance to the conditions obtaining in portal cirrhosis. Complete obstruction of the portal vein and abdominal vena cava resulted in only minimal hepatic lymph flow (approximately 350 cc. daily). That such large volumes of hepatic lymph flow may occur, however, suggests that lymphatic drainage may be a more important pathway of reabsorption from the peritoneal cavity than has been recognized previously. It should also be noted that these findings are somewhat at variance with those of Starling[3] who found marked increases in thoracic duct lymph flow after occlusion of the portal vein. These increments in thoracic duct lymph flow could be eliminated by ligature of the hepatic lymphatics.

Some comment on portal hydrostatic versus osmotic pressure is pertinent here. Obviously these forces do not remain static throughout the portal capillary system. Whereas the arterial portion of the splanchnic capillary may be characterized by a hydrostatic pressure which exceeds the osmotic pressure, water and some solid thereby being lost from the capillary, the venous portions, because of loss of water in excess of solids, will contain fluid of progressively higher osmotic pressure. It is entirely possible then that significant reabsorption of water into venous portions of splanchnic capillaries may occur because of an increase in osmotic pressure up to and above the hydrostatic pressure. The Starling hypothesis should be as valid in the portal system as elsewhere in the body.

SUMMARY

Six patients with ascites have been studied, four with portal cirrhosis and two with peritoneal carcinomatosis. It has been shown in these patients, using tritium-labeled water, that the water content of ascitic fluid enters and leaves the peritoneal cavity at a very rapid rate, approximating 40 to 80 per cent per hour. Ascitic fluid, then, is a rapidly circulating medium rather than a segregated reservoir.

The peritoneal surfaces of both normal and diseased individuals are capable of reabsorbing large volumes of fluid. Not until the rate of inflow exceeds this maximum reabsorptive capacity, here designated as the ascites threshold, does ascites result. Using this principle the presence or absence of ascites in a variety of apparently contradictory conditions becomes more easily understandable.

REFERENCES

1. Peters, J. P. The problem of cardiac edema. *Am. J. Med.*, 12: 1, 1952.
2. Mankin, H. and Lowell, A. Osmotic factors influencing the formation of ascites in patients with cirrhosis of the liver. *J. Clin. Investigation*, 27: 145, 1948.
3. Starling, E. H. The Fluids of the Body. The Herter Lectures. (New York, 1908.) Chicago, 1909. W. T. Keener & Co.
4. Farnsworth, E. B. and Krakusin, J. S. Electrolyte partition in patients with edema of various origins. Qualitative and quantitative definition of cations and anions in hepatic cirrhosis. *J. Lab. & Clin. Med.*, 33: 1545, 1948.
5. Faloon, W. W., Eckhardt, R. D., Cooper, A. M. and Davidson, C. S. The effect of human serum albumin, mercurial diuretics and a low sodium diet on sodium excretion in patients with cirrhosis of the liver. *J. Clin. Investigation*, 28: 595, 1949.
6. Ralli, E. P., Robson, J. S., Clark, D. and Hoagland, C. L. Factors influencing ascites in patients with cirrhosis of the liver. *J. Clin. Investigation*, 24: 316, 1945.
7. Patek, A. J., Mankin, H., Colcher, H., Lowell, A. and Earle, D. P., Jr. The effects of intravenous injection of concentrated human serum albumin upon blood plasma, ascites and renal functions in three patients with cirrhosis of the liver. *J. Clin. Investigation*, 27: 135, 1948.
8. Siri, W. To be published.
9. Prentice, T. C., Siri, W., Berlin, N. I., Hyde, G. M., Parsons, R. J., Joiner, E. and Lawrence, J. H. Studies of total body water with tritium. *J. Clin. Investigation*, 31: 412, 1952.
10. Hevesy, G. and Zerahn, K. Determination of the blood corpuscle content. *Acta physiol. Scandinav.*, 4: 376, 1942.
11. Berlin, N. I., Huff, R. L., VanDyke, D. C. and Hennessy, T. G. The blood volume of the adult rat as determined by Fe^{59} and P^{32} labeled red blood cells. *J. Lab. & Clin. Med.*, 36: 435, 1950.
12. Berlin, N. I., Lawrence, J. H. and Gartland, J. The blood volume in chronic leukemia as determined by P^{32} labeled red blood cells. *J. Lab. & Clin. Med.*, 36: 435, 1950.
13. McKee, F. W., Schloerb, P. R., Schilling, J. A., Tishkoff, G. H. and Whipple, G. H. Protein metabolism and exchange as influenced by constriction of the vena cava. *J. Exper. Med.*, 87: 457, 1948.
14. Hahn, P. F., Miller, L. L., Robscheit-Robbins, F., Bale, W. F. and Whipple, G. H. Peritoneal absorption; red cells labeled by radio-iron hemoglobin move promptly from peritoneal cavity into circulation. *J. Exper. Med.*, 80: 77, 1944.
15. Cunningham, R. S. The physiology of the serous membranes. *Physiol. Rev.*, 6: 242, 1926.
16. McKee, F. W., Wilt, W. G., Hyatt, R. E. and Whipple, G. H. The circulation of ascitic fluid. *J. Exper. Med.*, 91: 115, 1950.
17. McKee, F. W., Yuile, C. L., Lamson, B. G. and Whipple, G. H. Albumin and globulin circulation in experimental ascites. *J. Exper. Med.*, 95: 161, 1952.
18. Volwiler, W., Bollman, J. L. and Grindlay, J. H. A comparison of two types of ascites. *Proc. Staff Meet., Mayo Clin.*, 25: 31, 1950.

Experience with Needle Liver Biopsies at the Hepatitis Center for Japan and Korea, 1950–1951*

CAPT. STEPHEN H. DESCHAMPS, M.C. *and* LT. COL. ARTHUR STEER, M.C.

Fort Dix, New Jersey *Tokyo, Japan*

WIDESPREAD experience has firmly established the use of needle liver biopsy in the diagnosis and clinical management of hepatic disease. Although successfully employed as early as 1893–1895,[23,38] the real impetus to the use of this procedure began with the work of Iversen and Roholm[26,47] in 1939 and increased very rapidly during and after World War II.[6–8,15,24,33,49] The usefulness of liver biopsy in the differential diagnosis of jaundice,[44,56] the evaluation of specific therapeutic regimens[13,29,54] and the elucidation of late sequelae of infectious hepatitis[12,31,32,51,53] has been amply attested by recent reports comprising thousands of cases.

In September, 1950, the 35th Station Hospital was established as a "Hepatitis Center" for the Far East Command in anticipation of the epidemic proportions assumed by infectious hepatitis among military personnel under conditions of combat.[2,14,16] During the period from September 1, 1950, to June 1, 1951, 2,351 cases of liver disease were seen at this hospital. The number of patients with hepatitis, cirrhosis and other diseases is given in Table I. Detailed studies of the epidemiology, clinical course and management of these cases are now in progress.†

The purpose of the present paper is to describe the use of the needle liver biopsy as a clinical tool, not only in diagnosis but also in helping to determine the therapeutic management and disposition of military patients at a hospital center in an overseas theater during an active and fluid military campaign.

INDICATIONS FOR BIOPSY

Eighty-four liver biopsies were performed on seventy-three patients during the period from September 1, 1950, to June 1, 1951. Although the information thus obtained was of great value in the care of these patients, they comprised only some 3.1 per cent of the total admissions during this period. The remaining patients, for the most part, suffered from uncomplicated typical viral hepatitis and recovery was complete and uneventful.

TABLE I
ADMISSIONS FOR HEPATIC DISEASE, 35TH STATION HOSPITAL, SEPTEMBER 1, 1950, TO JUNE 1, 1951

Final Diagnosis	No. of Patients	
Viral hepatitis		2,030
Infectious	2,011	
Homologous serum	19	
Cirrhosis (all types)		4
Hemolytic jaundice (including malaria)		7
Suspected hepatitis, no liver disease found		310
Total		2,351

Liver biopsy was performed in those cases in which (1) the diagnosis remained in doubt after considerable clinical and laboratory study; (2) recovery from a clinically typical attack of infectious hepatitis was unduly prolonged; (3) an attack of hepatitis had been unusually severe; and (4) there was a past history of recurrent jaundice. (Table II.) These indications were generally involved with the question of disposition of the patient, particularly when

† A preliminary survey and analysis of the activities of the Hepatitis Center, including a summary of the epidemiology and clinical features of this epidemic, was made in April, 1951, by Dr. W. Paul Havens, Jr.[20]

* From the Medical Service, 35th Station Hospital (Hepatitis Center, Japan Logistical Command, FEC), and the Department of Pathology, 406th Medical General Laboratory. Presented in part in a Symposium on Hepatitis, Japan Logistical Command Joint Medical Conference, Association of Military Surgeons of the United States, Osaka Army Hospital, Osaka, Japan, March 23, 1951. Published under the auspices of The Surgeon General, U. S. Army, who does not necessarily assume responsibility for the professional opinions expressed by the authors.

recovery was delayed and when the illness was unduly severe.

Diagnosis. These thirty-five patients are discussed later in the article.

Prolonged Disease. Recovery was considered delayed in these patients because liver function

TABLE II
INDICATIONS FOR BIOPSY IN SEVENTY-THREE PATIENTS

	No. of Patients	No. with Repeat Biopsy
Diagnosis	35	3
Prolonged disease	27	4
Severe disease	8	2
To assess therapy (control prior to treatment)	3	2
	73	11

tests, particularly the total serum bilirubin and the bromsulphalein dye retention, showed persistently abnormal* results, or because of the persistence of abnormal physical findings. Liver biopsy findings in such patients were not uniform. In some there was evidence of chronic hepatic disease while others showed only mild inflammatory activity without evidence of chronic disease. Further, some of the patients with biopsies showing chronic hepatic disease gradually improved and apparently progressed to complete clinical recovery while others required further hospitalization and study in the United States. Those patients whose biopsy did not show evidence of chronic hepatic disease progressed to complete recovery and ultimate return to full duty. Thus liver biopsy was useful in avoiding unnecessary evacuation of trained personnel and loss of their services in this theater at a critical time, and at the same time permitted study of patients requiring prolonged observation and treatment.

Severe Disease. In patients with hepatitis of unusual severity liver biopsy sometimes revealed rather extensive changes even after recovery seemed complete by physical examination and laboratory study. Such patients undoubtedly would not have fared well had they returned to full duty, which often meant combat assignments in Korea. These patients were therefore placed on limited duty for periods of three to six months to insure a convalescent period of relatively restricted physical activity and adequate diet. They were then readmitted for examination, laboratory studies and repeat biopsy, and their final disposition was again considered. The frequent lack of correlation between hepatic function as determined by laboratory tests and liver structure as seen on biopsy has been reported by others[23,35,45] and indicates the value of performing liver biopsy after recovery from unusually severe hepatitis, even when such "recovery" has been rapid and seems complete by the usual clinical criteria. Four patients with severe hepatitis who thus far have returned after a period of limited duty were still asymptomatic and had normal liver function tests. The liver biopsy in each case showed improvement. It was thus possible to retain certain patients for at least limited duty in this theater without deterioration of their hepatic status. Liver biopsy was instrumental in the selection of these patients.

Examination of liver tissue was also valuable in resolving the question of "chronic hepatitis" and/or "residual fibrosis" in certain cases with a history of "hepatitis" one or more times in the past. These patients presented symptoms

TABLE III
DISPOSITION OF PATIENTS BIOPSIED

Evacuated to United States	14
Limited duty (to be re-evaluated)	18*
From limited duty to full duty (after re-evaluation)	3
To full duty (chronic disease excluded)	34
Still in hospital	4†
Total	73

* According to follow-up information available in May, 1952 (from Lt. Col. Robert S. Jordan, MC, Chief of Medicine, 35th Sta. Hosp.), ten of these patients were discharged to full duty upon re-evaluation after their period of limited duty, one patient remained on limited duty for another 3 months and was then sent to full duty after a third biopsy and re-evaluation, two patients were evacuated to the United States and one patient placed on permanent limited duty. The remaining four patients in this group were lost to follow-up.

† Follow-up information in May, 1952 disclosed that one of these patients was evacuated to the United States, one progressed from limited to full duty after re-evaluation, and two are still on limited duty at last report.

* Normal values used at the Hepatitis Center were: (1) Total Serum Bilirubin: under 1.14 mg. per cent (Ducci and Watson modification of Malloy and Evelyn method[41] using the Coleman, Jr., spectrophotometer);[9] (2) Bromsulphalein Dye Test: 5 per cent or less retention forty-five minutes after injecting 5 mg./kg. body weight; (3) Alkaline Phosphatase: 1.5 to 4.0 Bodansky units;[5,11] (4) Cephalin-cholesterol Flocculation: ± or less in twenty-four and 2 plus or less in forty-eight hours;[18] (5) Thymol turbidity: under 4.0 units.[37]

which were often vague and suggestive of psychogenic gastrointestinal syndromes. Physical examination usually revealed only slight, if any, hepatomegaly without evidence of liver disease. Liver function tests were generally normal. Liver biopsy in such patients completed the exclusion of chronic disease.

Therapy Evaluation. Finally, serial liver biopsies were performed to assess the results of therapy in certain cases in which the finding of fatty metamorphosis on initial biopsy led to the use of lipotropic agents and in the evaluation of other drugs not heretofore used routinely in the management of infectious hepatitis. Table III lists the disposition of the biopsied patients.

TECHNIC

Progressive refinements in technic have decreased markedly the percentage of unsuccessful attempts and have enhanced greatly the safety with which needle biopsy may be done. The mortality of 0.5 per cent given in one report[52] has been reduced to zero in recent reports.[44,48,56] However, it must be borne in mind constantly that one can never completely divorce this procedure from the inherent peril of massive hemorrhage. Liver biopsy should therefore not be attempted without due precautions and adequate preliminary investigation.

Table IV lists the accepted contraindications to needle liver biopsy. Of these a bleeding tendency is most important. All patients had a bleeding, clotting and prothrombin time twenty-four to forty-eight hours prior to biopsy. Two pints of blood were cross matched and kept in readiness until twenty-four hours after the biopsy. A prolonged prothrombin time on initial examination was not an absolute contraindication if it could be corrected by parenteral administration of vitamin K or by blood transfusion. All patients received 16 mg. menadione® intramuscularly twice daily for forty-eight hours prior to and twenty-four hours following biopsy, as a precautionary measure. After biopsy patients were kept at strict bedrest for twenty-four hours, with observation of pulse and blood pressure hourly for the first twelve hours and every two hours for the next 12 hours.

All biopsies were performed with the Vim-Silverman needle using the intercostal approach. In one patient a subcostal biopsy was also performed because of striking enlargement of the left lobe of the liver, which extended 10 cm. below the xiphoid process (Case IV). Recent reports[10,48] also recommend the intercostal approach, reserving the subcostal or subxiphoid technics for those cases in which the liver is markedly enlarged or when nodules are present and are biopsied to exclude a malignant process.

TABLE IV
CONTRAINDICATIONS TO LIVER BIOPSY

General contraindications
- Hemorrhagic diathesis (if not reversible by parenteral vitamin K or blood transfusion)

Special contraindications
- Amebiasis or other disease which may be spread by biopsy (prior treatment necessary)
- Ascites (paracentesis prior to biopsy)
- Suspected abscess of liver or subphrenic space
- Severe or prolonged extrahepatic obstruction (danger of bile peritonitis)
- "Individual": debility, apprehension, lack of cooperation, etc.

Contraindications to intercostal and subcostal approach

Intercostal approach:
- Marked pulmonary emphysema
- Deformity of thoracic cage with loss of accessible intercostal space
- Disease of right lower lobe or pleura

Subcostal or xiphoid approach:
- Liver margin less than 15 cm. below costal margin
- Disease of or involving peritoneum (inflammatory or malignant)

A special feature of the technic used was the preliminary introduction of a No. 20 gauge, spinal puncture needle following injection of novocain. With this needle one could ascertain the adequacy of the anesthesia and verify the direction of and distance to the liver by the motion transmitted to the needle during respiration. Transmitted respiratory motions were perceptible when the tip of the needle pierced the diaphragm (the liver lying immediately beyond). This step avoided subsequent withdrawing movements by the patient because of inadequate anesthesia as well as unnecessary and dangerous exploration with the No. 15 gauge Vim-Silverman needle. The hazard of laceration in the final step was thereby reduced.

No untoward incident was encountered in our series. Three biopsies were abandoned because of extreme apprehension and consequent lack of cooperation despite the routine administration of preliminary sedation (demerol® 75 mg. or sodium luminal 120 mg. intramuscularly). A few patients experienced mild epigastric and/or right upper quadrant discomfort after biopsy. Occasionally mild diaphragmatic pleurisy was encountered. In no instance were

the symptoms severe and none lasted more than a few minutes to two hours following the procedure.

PATHOLOGY

The liver biopsy specimens were immediately placed in 10 per cent formalin and in Carnoy's solution. The latter fixative was used exclusively after the first few specimens. In a few cases glycogen studies were performed (Best's carmine stain on absolute-alcohol fixed portions of the specimen) but this added little information in these cases and was not done routinely.

TABLE V
DIAGNOSES USED FOR LIVER BIOPSIES

Hepatitis, active
Postnecrotic scarring
Fatty metamorphosis
Portal cirrhosis
Hepatitis of specific etiology (e.g., tuberculous, amebic)

After the usual preparation paraffin sections were stained with hematoxylin and eosin, and by Masson's trichrome method. The slides were interpreted first without reference to the history and clinical findings and again after this information was studied. All sections were reviewed by both authors and were submitted to the Registry of Hepatic Pathology at the Armed Forces Institute of Pathology.

Originally, a detailed classification based in part on reports in the literature was used. After correspondence with the Registry of Hepatic Pathology a slightly modified version of the classification used there was substituted. The result was a simple list of diagnoses (Table v) based primarily on morphologic changes with little emphasis placed on etiology except where a specific diagnosis was possible. The amount and extent of inflammatory reaction and the presence of scarring were the important criteria. This, then, was a working classification valuable in determining diagnosis and in determining the necessity for further therapy, retention in the theater, or return to the United States.

Originally, the diagnoses of "focal necrosis," "portal hepatitis" and "cholangiolitic hepatitis" were also used. Later these were included under the one term "active hepatitis." This diagnosis was made when diffuse active inflammation, focal necrosis and/or bile stasis in the smallest biliary radicles was present. The diagnosis of postnecrotic scarring indicated the presence of definite fibrosis and inflammation in the portal areas sometimes accompanied by bile duct proliferation. In some sections both active hepatitis and postnecrotic scarring were present. Postnecrotic scarring was distinguished histologically from portal cirrhosis in that in the former the fibrosis was irregular, rather than diffuse, and generally not accompanied by pseudolobule formation. These criteria may not be valid for old cases of postnecrotic scarring which have progressed to actual cirrhosis. Histologically, distinction between a viral and a toxic etiology could not be made. Other terms in the list of diagnoses are self-explanatory.

TABLE VI
AGE AND RACE DISTRIBUTION OF PATIENTS WHO HAD LIVER BIOPSY

	Under 25	25–34	35–44	45	Total
Caucasian	38	19	8	1	66
Negro	1	4	1		6
Oriental		1			1
Total	39	24	9	1	73

RESULTS

The eighty-four biopsies comprising this series were performed in seventy-three patients, all of whom were males. The racial and age distribution, shown in Table VI, was similar to the over-all hospital admissions to the Hepatitis Center during this period.

Diagnosis. Obscure diagnosis was the chief indication for liver biopsy in thirty-five instances. In thirteen of these (37 per cent) the clinical diagnosis (taking the "majority consensus" recorded on the chart) was confirmed by the biopsy. The biopsy was credited with a precise diagnosis which had not been established by clinical methods in twelve cases (34 per cent). Eight other patients (23 per cent) had a history of jaundice in the past and presented vague gastrointestinal symptoms with slight hepatomegaly. They had no other evidence of chronic hepatic disease by physical or laboratory examinations. In all eight instances liver biopsy showed no abnormalities, suggesting that chronic hepatic disease was not the basis for their complaints. Finally, in two patients (6 per cent) the liver was essentially normal on biopsy in spite of chronic, asymptomatic, low grade jaundice for many years. In these patients the liver biopsy

FIG. 1. Case I (J-2). Lymphocytic infiltration and scarring of portal area and mild fatty metamorphosis.

was not helpful in diagnosis except in a negative fashion.

The following cases are illustrative of instances in which liver biopsy aided materially in arriving at a precise diagnosis:

CASE I. (No. J-2.) A twenty year old white soldier was admitted because of diarrhea of three weeks' duration consisting of four to five watery and slimy movements daily without blood. There were associated para-umbilical cramps but no history of chills, fever, upper gastrointestinal symptoms or dark urine. The past history and systemic review were negative for symptoms suggesting hepatitis or other liver disease.

Physical examination revealed a firm, non-tender liver extending 3 cm. below the costal margin. Rectal and proctosigmoidoscopic examinations showed nothing unusual. Stool examinations were positive for ova of Ascaris but repeatedly negative for amebas. Amebic complement-fixation test was negative. The white blood count was 12,200, eosinophils 2 per cent. All liver function tests were normal except for BSP retention of 10 to 30 per cent in forty-five minutes and 3 plus cephalin-flocculation in forty-eight hours.

Liver biopsy (Fig. 1) revealed fibrosis, heavy infiltration of portal areas by lymphocytes and mild fatty metamorphosis of the parenchyma. The changes suggested chronic hepatitis with early cirrhosis of the postnecrotic type.

Comment. Although this patient's only symptom was diarrhea and there was no history of antecedent jaundice, significant alcohol intake, dietary insufficiency or exposure to hepatotoxins, liver biopsy revealed fairly advanced cirrhosis suggestive of "toxic nodular cirrhosis." The ascariasis was not considered contributory to the patient's liver disease and was readily eliminated by hexylresorcinol. The patient was evacuated to the United States.

CASE II. (No. J-86.) A twenty-five year old Negro soldier was evacuated from Korea with vague gastrointestinal complaints of two months' duration consisting of epigastric cramps and occasional vomiting unrelated to food. There were no chills, fever, cough or night sweats. Physical examination was negative except for shotty, discrete and non-tender cervical and axillary lymph nodes.

Chest x-ray showed bilateral hilar lymphadenopathy; the lung fields were clear. The gastrointestinal tract was normal radiologically and x-rays of the hands revealed no lesions suggestive of sarcoidosis. Complete blood count was normal but the sedimentation rate was persistently elevated to 30 to 40 mm. at one hour. The serum proteins were normal and except for a thymol turbidity of 6.2 units all liver function tests were within normal limits. Tuberculin test was negative in first and second strength PPD.

While in the hospital the patient was asymptomatic but exhibited a low grade fever of 100° to 101°F. each afternoon. Sarcoidosis was

FIG. 2. Case III (J-10). Pseudolobule formation, fibrosis and active inflammation in periphery of lobule associated with an increase in small bile ducts.

suspected because of the patient's race, hilar adenopathy and negative tuberculin tests. None of the peripheral lymph nodes was deemed sufficiently enlarged to justify excision for diagnosis.

Liver biopsy revealed many discrete granulomatous foci scattered throughout the hepatic parenchyma. These consisted of epithelioid cells and lymphocytes with a fine stroma of connective tissue. No giant cells were seen. There was no caseation.

Comment. The lesions described were consistent with those of Boeck's sarcoid. As has been pointed out by Klatskin and Yesner,[30] these granulomatous foci are indistinguishable histologically from those produced in a number of other conditions, including brucellosis, miliary tuberculosis and erythema nodosum. Subsequent to liver biopsy swelling and tenderness of both parotid glands developed without evidence of uveitis. The patient was evacuated to the United States.

CASE III. (No. J-10.) A forty-four year old white soldier was evacuated from Korea in November, 1950, with a diagnosis of infectious hepatitis. He complained of fatigability and progressive anorexia for one month followed by the appearance of dark urine, acholic stools and jaundice during the week preceding his evacuation to the Hepatitis Center. Further questioning revealed that the patient had been a Japanese prisoner of war for thirty-nine months, during which time he had had beri-beri as well as nutritional edema. He admitted consuming an average of twelve beers daily but denied any gastrointestinal symptoms and claimed to have taken an adequate diet from 1946 until the present illness began.

Physical examination revealed an emaciated male appearing much older than his stated age. There was mild dermal and scleral icterus, sparse body hair and many spider angiomas. No gynecomastia was present. The superficial abdominal veins were dilated. The liver was firm, finely nodular and non-tender, extending 4 cm. below the costal margin. The spleen was just palpable. Testes were markedly atrophic.

Laboratory data were typical of hepatocellular jaundice; A/G ratio was normal. Esophageal varices were not demonstrated radiologically.

The clinical diagnoses were: (1) Laennec's cirrhosis and (2) superimposed viral hepatitis.

Liver biopsy (Fig. 2) showed extensive fibrosis with increased numbers of small bile ducts and distortion of the lobular architecture by broad bands of connective tissue in which heavy cellular infiltration was noted. Areas of hepatic cell regeneration were also noted. The glycogen content seemed diminished but fatty vacuolization was not seen.

Comment. The histologic findings suggested "toxic nodular cirrhosis" rather than ordinary "portal" (Laennec's) cirrhosis. The former has been described as occurring after non-fatal, acute infectious hepatitis with massive hepatic

necrosis (acute or subacute yellow atrophy) and has also been produced experimentally in rats by Himsworth[21] and by György[17] with diets deficient in sulfhydryl groups. Although this patient gave no history of antecedent hepatitis, the history of prolonged, extreme nutritional deficiency during World War II parallels to some extent the experimental conditions leading to massive hepatic necrosis and subsequent cirrhosis of the type described.[22]

This patient was given a high protein, high calorie diet with supplementary vitamin B complex, brewer's yeast (12 gm. daily) and choline (2 gm. daily). His appetite improved but jaundice persisted. He was evacuated to the United States.

Case IV. (No. J-59.) A twenty-eight year old white soldier was evacuated to Japan in March, 1951. Present illness began insidiously four months previously with increasing fatigability punctuated by an episode of fever lasting four days, which subsided without therapy. In February, 1951, two months after onset, he sought medical advice and was found to have an enlarged liver and mild secondary anemia. There was no history of gastrointestinal symptoms either before or during the present illness and no weight loss, dark urine, acholic stools or jaundice. No family history of jaundice or history of exposure to hepatotoxins, blood, plasma or parenteral therapy was elicited.

Physical examination revealed no weight loss or jaundice. There were many spider angiomas but no hair loss, lymphadenopathy, collateral venous circulation, gynecomastia or testicular atrophy was found. The left lobe of the liver was strikingly enlarged and extended 10 cm. below the xiphisternum into the left upper quadrant. The edge was sharp and stony hard with an irregular anterior convexity suggesting a large nodule. The right lobe descended only 2 cm. below the costal margin. The spleen was palpable 2 to 3 cm. below the left costal margin and was firm and non-tender.

On March 29, 1951, serum bilirubin was 0.26 mg. per cent at one minute with a total of 0.64 mg. per cent, BSP was 5 per cent (forty-five minutes), cephalin-flocculation was 1 plus in twenty-four hours and 4 plus in forty-eight hours, thymol turbidity was 10 units, alkaline phosphatase was 4.3 Bodansky units, serum albumin 4.3 gm. per cent with globulin 3.7 gm. per cent and total cholesterol was 280 mg. per cent. The red blood count was 3.69 million per cu. mm. and hemoglobin 13.0 gm. per cent; white blood count was 4,800 per cu. mm. with normal differential count. Gastrointestinal series showed nothing unusual. The clinical diagnoses included possible primary malignancy of liver or toxic nodular cirrhosis.

Table VII

FINDINGS IN PATIENTS WITH PROLONGED OR SEVERE DISEASE (AT TIME OF BIOPSY)

Abnormal liver function tests only*	13
Abnormal liver function tests plus abnormal physical findings*	18
Hepatomegaly	13
Spider angiomas	5
Abnormal physical findings only	4
Hepatomegaly	2
Hepatosplenomegaly	1
Spider angiomas	1
Total	35

* Chiefly, BSP retention only (fourteen cases) or BSP retention plus slightly elevated total serum bilirubin (eleven cases). The remaining six patients had various other combinations of abnormal tests.

Liver biopsy was performed April 3rd and both intercostal and subxiphoid specimens were obtained, the latter from the nodular convexity in the left lobe. The first (intercostal) specimen revealed only a few foci of necrosis with infiltration by small numbers of lymphocytes and polymorphonuclear cells. The other specimen, however, showed lobular distortion by wide bands of connective tissue partially circumscribing the lobules in some sections. Small bile ducts were increased in number. These changes were interpreted as indicating severe postnecrotic scarring.

Comment. This case illustrates two points: (1) the existence of advanced cirrhosis of the toxic nodular variety which involved one lobe of the liver and which had caused portal hypertension, in the complete absence of any history of antecedent hepatitis, jaundice or dietary insufficiency, and (2) the possibility of being misled by the liver biopsy in instances in which the hepatic lesion is not diffuse.

Prolonged and/or Severe Disease. These two combined were the indications for biopsy in thirty-five of the seventy-three patients in this series. The abnormalities present at the time of biopsy in this group of patients are listed in Table VII. An analysis of the *predominant* histologic changes, using the criteria already described, showed continued activity (active hepatitis) in twenty-one instances, postnecrotic scarring in eight instances and fatty metamorphosis in six instances.

The laboratory data in this series were not sufficient to attempt an extensive correlation between the laboratory studies and pathologic changes observed on biopsy. However, no single histologic finding or group of findings appeared to be consistently associated with any combination of physical findings or abnormal laboratory tests. This is in keeping with more extensive studies in which such correlation was attempted. Although some observers[27,42,44,46] have reported statistically significant correlations, others[35,38,51,53] have been unable to confirm such observations. Table VIII shows the changes found in six patients who had repeat biopsies from three to sixteen weeks after original biopsy. All were patients with severe or prolonged disease. Three are among the patients described in more detail hereafter.

TABLE VIII

CHANGES ON REPEAT BIOPSY IN SIX PATIENTS ORIGINALLY BIOPSIED BECAUSE OF PROLONGED OR SEVERE DISEASE

No.	First Biopsy*			Second Biopsy*			Weeks from Onset to First Biopsy	Weeks from Onset to Second Biopsy	Weeks between Biopsies
	AH	FM	PNS	AH	FM	PNS			
J-28 (Case VI)	+	++	±	±	0	+	6	16	10
J-37 (Case VIII)	++	±	+	+	+	+	8	11	3
J-19	+	++	±	±	+	0	11	27	16
J-40 (Case IX)	++	0	+	±	0	+	13	23	10
J-58	+++	0	+	++	0	±	6	12	6†
J-29	+	0	++	+	0	0	18	33	15

* Severity graded 1 to 4 plus.

Legend: AH = active hepatitis; FM = fatty metamorphosis; PNS = postnecrotic scarring.

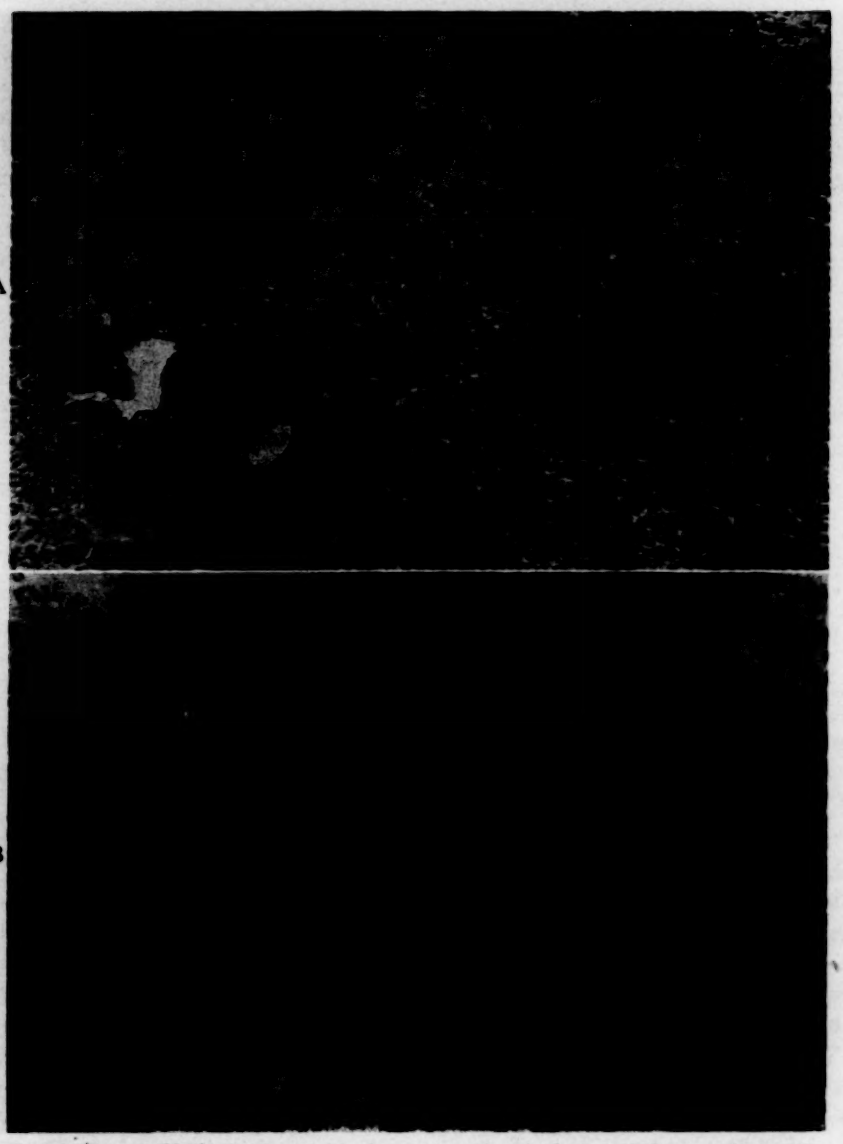
† A third liver biopsy in this patient was obtained fifteen weeks after the second biopsy (twenty-seven weeks after onset). This revealed ± active hepatitis, 0 fatty metamorphosis and probably *no* true PNS but only some mild stromal collapse.

CASE V. (No. J-8.) A twenty year old white soldier, in whom typical acute infectious hepatitis developed in early October, 1950, was evacuated from Korea about one week after onset. Despite the rapid return of appetite and well-being, deep jaundice, biliuria and marked hepatic enlargement were still present six weeks after onset. There was no splenomegaly or other abnormal physical findings. Serum bilirubin averaged 7.0/15.0 mg. per cent (1 min./total) with 4 plus cephalin flocculation and 20.0 units thymol turbidity. Alkaline phosphatase was 9.0 Bodansky units and urobilinogen was present in the urine in 1:20 dilution.

Liver biopsy (Fig. 3A) showed lymphocytic infiltration in portal areas, with slight increase of connective tissue and small bile ducts. Many inspissated bile-plugs (Fig. 3B) were noted.

Comment. This patient's illness was characterized by a prolonged phase of "cholangiolar obstruction." The presence of bile pigments in the feces and urobilinogen in the urine indicated that this obstruction was not complete. The involvement of portal triads and the presence of inspissated bile were consistent with the clinical observations of prolonged jaundice and biliuria. This phase of hepatitis is usually much more brief in the average case[10,19] and when it persists for this length of time must be differentiated from extrahepatic obstruction or chronic cholangiolitic hepatitis.[55] The liver biopsy excluded such changes. The patient ultimately made a complete recovery and was discharged to full duty after twelve weeks' hospitalization. Follow-up report from another hospital three months later revealed that the patient was asymptomatic with negative physical examination and completely normal liver function tests.

Fatty metamorphosis is rarely mentioned in the literature as a frequent occurrence during the acute stage, in convalescence or as a late residual finding in the course of infectious hepatitis.[44] However, significant degrees of fatty metamorphosis were noted in six patients, comprising 17 per cent of the cases biopsied because of prolonged and/or severe disease. In two instances all liver function tests were normal and persistent hepatomegaly was the sole abnor-



3A

3B

FIG. 3. Case V (J-8). A, six weeks after onset of typical acute infectious hepatitis; focal necrosis, with inflammation in periphery of lobules. B, same case; bile plugs in small biliary radicles.

mality on physical examination. Three patients presented persistently abnormal BSP retention without other abnormalities. One patient (Case VII) had both hepatomegaly and spider angiomas as well as abnormal liver function tests. It may be significant that this patient admitted a considerable indulgence in alcohol during his convalescence from hepatitis.

Rapid improvement, both clinically and on biopsy, was the rule in these cases following treatment with lipotropic agents. The uniformity and speed of response appeared to parallel reported experience with lipotropic substances in fatty metamorphosis of the liver associated with alcoholism and dietary insufficiency.[13,54] Progression to diffuse hepatic fibrosis has not been observed in any of our patients to date.

CASE VI. (No. J-28.) An eighteen year old white man had viral hepatitis in October, 1950, while in Korea. There was no history of alcoholic excesses or dietary irregularity in the past. Jaundice disappeared by the fourth week after onset and the patient felt well, exhibiting an excellent appetite and steady gain in weight. In the sixth hospital week, despite continuation of bedrest, the liver still remained enlarged 4 to 6 cm. below the costal margin, with persistent

tenderness. There was no splenomegaly or spider nevi. The BSP was 5 per cent (forty-five minutes) and bilirubin normal; cephalin flocculation was plus/minus at twenty-four hours and 2 plus at forty-eight hours, and thymol 7.0 units.

Liver biopsy six weeks after onset of illness revealed normal architecture and minimal increase in portal connective tissue with mild inflammatory cell infiltration. Moderate fatty metamorphosis was present.

The patient was given choline (2.0 gm. daily) and was discharged to limited duty. He took choline for thirty days and remained on limited duty for three months. At that time he was readmitted. He was entirely asymptomatic, the liver was neither enlarged nor tender and all tests were normal.

Liver biopsy sixteen weeks after onset of illness showed occasional foci of necrosis but the architecture was again normal. Fatty metamorphosis had disappeared. There was a slight increase in portal scarring. The patient was discharged to full duty.

CASE VII. (No. J-55.) A twenty-seven year old white Army sergeant had hepatitis with mild jaundice in mid-November, 1950, while in Korea. History revealed a moderate indulgence in alcohol but his diet was adequate and he had had no previous gastrointestinal symptoms. By early January, 1951, the liver was no longer enlarged or tender and the serum bilirubin had returned to normal. However, the BSP test remained elevated (30 per cent). In February, despite continued well-being and an excellent appetite, spider angiomas appeared and the liver again became palpable 2 to 5 cm. below the costal margin. BSP had remained abnormal throughout this time.

Liver biopsy (Fig. 4) on March 20th revealed extensive fatty metamorphosis although lobular architecture was preserved and only one of several portal areas showed an increase in connective tissue and bile ducts.

Choline therapy was initiated and the patient evacuated to the United States.

Postnecrotic Scarring. In spite of the extensive experience with liver biopsy reported in the literature the exact pathogenesis of so-called "toxic nodular cirrhosis" is still not definite. It is, however, generally accepted as following non-fatal massive hepatic necrosis or "subacute yellow atrophy" which characterizes the most severe instances of any type hepatitis. It has not been shown conclusively that viral hepatitis of a less serious degree can lead to cirrhosis of this type.

FIG. 4. Case VII (J-55). Extensive fatty metamorphosis.

The relation between viral hepatitis and portal cirrhosis is more confused. Lucké,[36] Havens[19] and others[28,40] believe that there is no such association. Bloomfield,[4] Howard and Watson,[25] Sherlock[51] and others,[1,3,31,34,43] although differing on details, form a group who believe that some cases of viral hepatitis have a prolonged course frequently associated with relapse, describe these cases as instances of chronic hepatitis and believe that typical portal cirrhosis develops in some of these patients.

Havens[19] has reviewed the biopsy findings in several series, both with and without recurrence of jaundice, over a period of follow-up as long as fifteen months and concluded that "essentially normal" hepatic parenchyma was the end result in most cases. Some changes of doubtful significance, such as periportal infiltration, could persist even in cases with a normal clinical recovery and no other evidence of active disease. Mallory[40] examined biopsy specimens in forty cases with prolonged recovery, as well as thirteen cases with one or more relapses, and found little evidence of chronic lesions such as fibrosis, pseudolobulation or increased bile duct proliferation in either group. Combining the series of Dible et al.,[8] Sherlock and Walshe[50] and Mallory,[40] only three cases of nodular cirrhosis were described in a total of 178 cases of non-fatal viral hepatitis. A higher incidence has been reported from the epidemics in Scandinavia[32] although Havens[19] pointed out the possible importance of case selection in this group. Koszalka[31] followed up 100 patients with

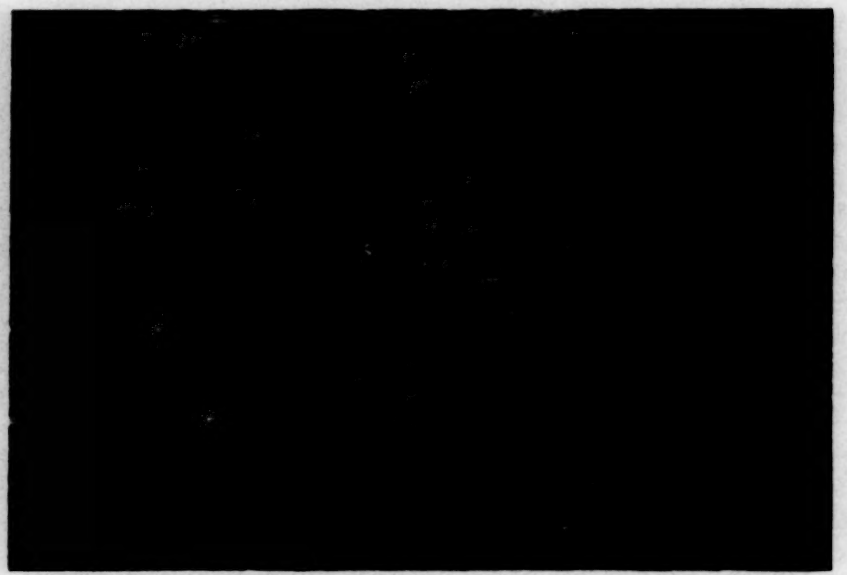


FIG. 5. Case VIII (J-37). Eight weeks after onset of acute hepatitis showing focal necrosis, lymphocytic infiltration and slight fatty metamorphosis.

infectious hepatitis and described the development of portal cirrhosis on serial biopsy in two cases. The interval between biopsies in these patients was only three to four weeks and neither the time interval nor the clinical data provided convincing support for the development of true cirrhosis. As discussed hereafter the possibility that the areas biopsied were not comparable or that the lesions found were not representative of the liver as a whole must be considered.[28]

Several instances of early "postnecrotic scarring" were found in the group biopsied because of prolonged and/or severe disease. These changes were present as early as three weeks after the onset of the first symptoms of hepatitis.

In two patients subjected to repeat biopsy (Table VIII, Cases J-29 and J-58) comparison of the serial change deserves special attention. The initial biopsy in each case (six and eighteen weeks after onset of hepatitis, respectively) revealed postnecrotic scarring. The second biopsy in each case (six and fifteen weeks, respectively, after the initial biopsy) showed diminution in the amount of scarring. One assumes that in dealing with a diffuse hepatic lesion such as infectious hepatitis these specimens are comparable, since the same general liver area was biopsied. If this is true, it would appear that increased fibrous tissue and other changes included in "postnecrotic scarring" are not necessarily irreversible and therefore may not always augur eventual cirrhosis. However, there is some indication that other factors are involved. Although viral hepatitis is usually a diffuse disease, there is some suggestion that even in the same area some lobules are more severely affected than others. This is especially true in non-fatal viral hepatitis. The postnecrotic scarring present could be irregular in distribution and amount. Comparative biopsies then may not give a true picture of the changes at various intervals. Further, it is difficult to determine how much of the fibrous tissue seen represents true scarring and how much represents collapse of stroma. These questions may be clarified as larger numbers of our patients return for repeat biopsy.

Other examples of the course and disposition of patients with prolonged disease or severe hepatitis, in which postnecrotic scarring was a prominent feature, are illustrated by the following:

CASE VIII. (No. J-37.) A white man age twenty-two years in whom jaundice developed on December 15, 1950, was hospitalized on December 27th. He denied any antecedent or associated symptoms. Jaundice remained deep (total serum bilirubin 23.6 to 19.4 mg. per cent) throughout January, 1951, although the patient was on bedrest, felt well and had an excellent appetite. The liver was enlarged and tender during this time. In early February anorexia and nausea developed associated with right upper quadrant pain and increased hepatic tenderness. Jaundice deepened slightly.

Liver biopsy (Fig. 5) on February 9th re-

vealed foci of necrosis, slight fatty metamorphosis and lymphocytic infiltration in the portal zones with mild portal fibrosis.

The patient received vitamin supplements and special diet therapy. His symptoms subsided within seven to ten days and recovery was thereafter rapid and uneventful. By March 1st the liver was neither enlarged nor tender and both bilirubin and BSP were normal.

Liver biopsy on March 1st showed a decrease in the inflammatory reaction; portal fibrosis was unchanged and there was a slight increase in fatty metamorphosis.

The patient was discharged to limited duty for follow-up studies in three months.

CASE IX. (No. J-40.) This patient was a twenty-one year old white man in whom infectious hepatitis developed in November, 1950. Although neither jaundice nor hepatomegaly was ever striking, his course was exceedingly prolonged and punctuated by episodes of anorexia and intermittent dyspepsia. At the time of biopsy in February, 1951, the liver was not enlarged or tender and there was no splenomegaly or spider nevi. The total serum bilirubin was still slightly abnormal (1.5 to 2.3 mg. per cent) and the BSP ranged between 13 and 25 per cent. Radiologic studies of gallbladder and gastrointestinal tract were negative.

Liver biopsy (Fig. 6) on February 16, 1951, three months after onset of hepatitis, revealed marked portal lymphocytic infiltration, an increase in the periportal connective tissue and some proliferation of bile ducts. Foci of necrosis were observed in the parenchyma.

Despite the addition of choline and vitamin supplements and continued bedrest the clinical status remained unchanged. Liver biopsy was repeated April 24th and again revealed evidence of postnecrotic scarring although the inflammatory reaction had regressed.

The patient was evacuated to the United States. Follow-up report in June, 1951, indicated that no significant improvement or deterioration had occurred.

CASE X. (No. J-47.) A thirty-five year old sergeant first noticed symptoms of hepatitis with moderate jaundice in November, 1950. The total serum bilirubin was 6.5 mg. per cent and fell to 4.7 mg. per cent in the third week of illness, at which time the patient felt well and seemed to be improving uneventfully. A severe relapse occurred about December 8th manifested by nausea and vomiting, fever of 102° to

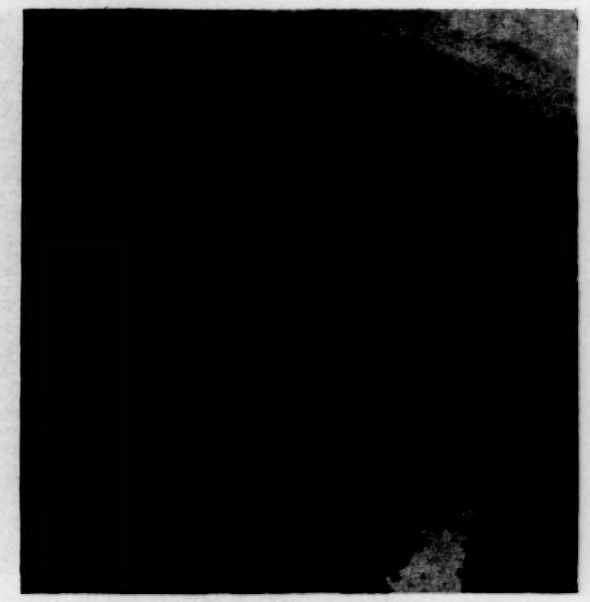


FIG. 6. Case IX (J-40). Focal necrosis, inflammation in portal zone and proliferation of small bile ducts.

103°F. and rapidly deepening jaundice. The liver was markedly enlarged (8 cm. below the costal margin) and very tender; the spleen was just palpable. There was no ascites or bleeding tendency. On December 10th the total serum bilirubin was 37.0 mg. per cent and the patient had a severe atonic ileus which for several days imitated an acute condition of the abdomen. He received large amounts of parenteral glucose and vitamin supplements. Hepatic coma seemed imminent but after a week improvement began and was thereafter steady. By mid-January, 1951, two months after onset of hepatitis and five weeks after the relapse, the bilirubin and BSP were normal and the patient was entirely asymptomatic, exhibiting an excellent appetite and progressive gain in weight.

At the time of biopsy on February 9th the liver was still palpable 3 cm. below the costal margin, with a firm, non-tender edge. There were no spider angiomas, splenomegaly or dilated abdominal veins. All liver function tests had remained normal after three weeks of full ambulation and one week of mess hall and pass privileges.

Liver biopsy (Fig. 7) twelve weeks after onset revealed extensive hepatic damage which included fatty metamorphosis, periportal fibrosis and increased numbers of small bile ducts.

The patient was discharged to limited duty. He has not yet returned for re-evaluation.

Comment. This case illustrates the finding of

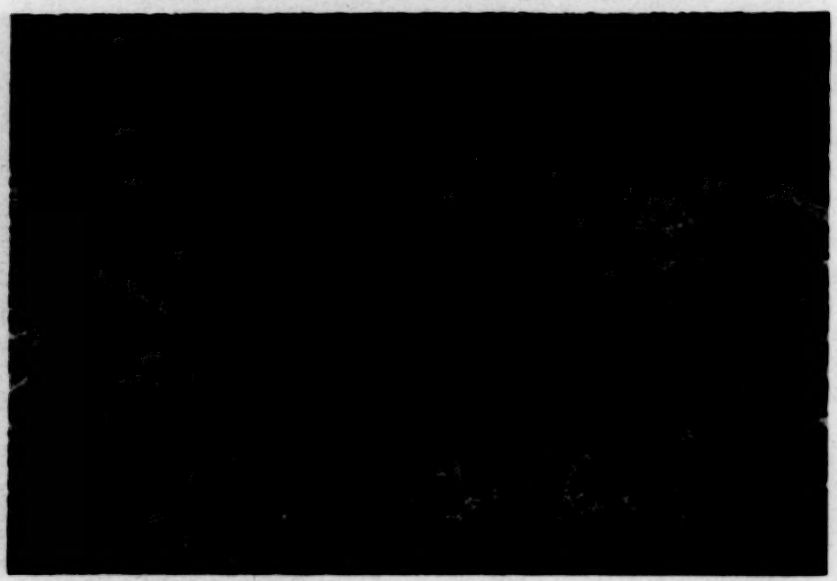


FIG. 7. Case x (J-47). Biopsy twelve weeks after onset of hepatitis showing fibrosis in portal area, inflammatory reaction and an increase in bile ducts. Fatty metamorphosis is not prominent in this area.

extensive changes on liver biopsy at a time when "clinical" recovery seemed complete except for residual hepatomegaly.

Liver biopsy in these three cases showed evidence of persistent severe damage although the patients differed in the course of their illness and in clinical findings. Case VIII had a chronic illness with persistently abnormal physical findings during which he had an exacerbation of his symptoms. Case IX had a chronic but not particularly severe illness. Case X had a course only slightly prolonged over the average but punctuated by severe relapse.

Recurrences ("*Relapses*"). Seven patients with hepatitis seen during the period covered by this report were considered to have had relapses or exacerbation of their illness. In four cases (including Cases VIII and X) episodes of increasing jaundice and anorexia occurred during the course of their disease. The other three patients had recurrences of anorexia and other gastrointestinal symptoms, biliuria and jaundice after apparently complete recovery from the initial attack three to twelve weeks following discharge from the hospital.

Liver biopsy performed two to eight weeks after onset of the initial attack in three of the four patients with exacerbation of symptoms revealed the usual changes of "active hepatitis" with focal necrosis and cellular infiltration. The fourth of these patients (Case X) showed postnecrotic scarring and fatty metamorphosis after recovery from the relapse. (Fig. 7). One patient (Case VIII) showed inflammatory changes at the time of relapse, and on rebiopsy three weeks after the relapse, an increase in fibrous tissue.

The three patients with late relapses had been entirely asymptomatic at time of discharge after an apparently rapid and uneventful recovery. Physical findings and laboratory tests had remained normal during a three-week period of progressive activity and physical reconditioning. They were readmitted three to twelve weeks after discharge with recurrence of symptoms. Physical examination showed tender hepatomegaly in all three patients and splenomegaly in one. None had spider angiomas or other suggestions of chronicity. Liver biopsy in all three cases revealed focal necrosis and portal inflammatory changes but no fibrosis, bile duct proliferation or fatty metamorphosis. All three patients recovered from this second episode within three to six weeks, with no residual abnormalities on physical examination or by laboratory tests of liver function.

SUMMARY

Eighty-four liver biopsies were performed in seventy-three patients in an army hospital in Japan. During this period 2,351 patients with liver disease were hospitalized. Diagnosis and the determination of the status of patients with prolonged and/or severe disease were the

important indications for biopsy. Underlying these indications was the necessity for determining the military disposition of these patients. In these problem cases liver biopsy proved to be of considerable value in reaching a decision.

No untoward incidents occurred in any of the patients who had liver biopsy. The technic is described.

The occurrence of postnecrotic scarring and fatty metamorphosis during attacks of viral hepatitis is described. Long follow-up studies will be required before the significance of these changes can be properly evaluated.

Acknowledgment: Appreciation is expressed to Major James B. Hartney, M.C., and Major Walter G. Olin, M.C., of the Department of Pathology, 406th Medical General Laboratory, who assisted in examining and interpreting the biopsy sections; Colonel Francis W. Pruitt, M.C., Consultant in Internal Medicine, GHQ, FEC for continued advice and invaluable assistance in guiding many of our clinical studies, and to Major Robert E. Campbell, M.C., Assistant Chief of Medicine, 35th Station Hospital, who performed many of the liver biopsies. The cooperation of Colonel Sterrett E. Dietrich, Commanding Officer, 35th Station Hospital, and Lt. Colonel R. L. Hullinghorst, Commanding the 406th Medical General Laboratory is also gratefully acknowledged. Technical assistance was ably rendered by S.F.C. Sybil Giles, WAC, of the Department of Pathology, 406th Medical General Laboratory, and Pfc. Virgil B. Truelove, AMEDS, 35th Station Hospital.

REFERENCES

1. Altschule, M. D. and Giligan, D. R. Chronic latent hepatitis following catarrhal jaundice. *New England J. Med.*, 231: 315, 1944.
2. Barker, M. H., Capps, R. B. and Allen, F. W. Acute infectious hepatitis in the Mediterranean theater, including hepatitis without jaundice. *J. A. M. A.*, 128: 997, 1945.
3. Barker, M. H., Capps, R. B. and Allen, F. W. Chronic hepatitis in the Mediterranean theater. *J. A. M. A.*, 129: 653, 1945.
4. Bloomfield, A. L. The natural history of chronic hepatitis (cirrhosis of the liver). *Am. J. M. Sc.*, 195: 429, 1938.
5. Bodansky, A. Phosphatase studies. II. Determination of serum phosphatase. Factors influencing the accuracy of the determination. *J. Biol. Chem.*, 101: 93, 1933.
6. Cogswell, R. C., Schiff, L., Safdi, S. A., Richfield, D. F., Kumpe, C. W. and Gall, E. A. Needle biopsy of the liver. *J. A. M. A.*, 140: 385, 1949.
7. David, W. D., Scott, R. W. and Lund, H. Z. Needle biopsy of liver. *Am. J. M. Sc.*, 212: 449, 1946.
8. Dible, J. H., McMichael, J. and Sherlock, S. Pathology of acute hepatitis: aspiration biopsy studies of epidemic, arsenotherapy and serum jaundice. *Lancet*, 2: 402, 1943.
9. Ducci, H. and Watson, C. J. Quantitative determination of the serum bilirubin with special reference to the prompt reacting and the chloroform soluble types. *J. Lab. & Clin. Med.*, 30: 293, 1945.
10. Ducci, H., Barabona, R. and Barzellato, J. The clinical course of hepatitis. *Gastroenterology*, 17: 45, 1951.
11. Fiske, C. H. and Subbarow, Y. The colorimetric determination of phosphorus. *J. Biol. Chem.*, 66: 375, 1925.
12. Flood, C. A. and James, E. M. Clinical and pathological findings in prolonged hepatitis. *Gastroenterology*, 8: 175, 1947.
13. Franklin, M., Salk, M., Steigmann, F. and Popper, H. Clinical, functional, and histological responses of fatty metamorphosis of human liver to liptotropic therapy. *Am. J. Clin. Path.*, 18: 273, 1948.
14. Gardner, H. T. A note on the history of epidemic viral hepatitis in Germany. *Am. J. Med.*, 8: 561, 1950.
15. Gillman, T. and Gillman, J. Modified liver aspiration biopsy apparatus and technique, with special reference to its clinical applications as assessed by 500 biopsies. *South African J. M. Sc.*, 10: 53, 1945.
16. Gould, R. L. Epidemiologic field studies of infectious hepatitis in the Mediterranean theater of operations. *Am. J. Hyg.*, 43: 1946. I. Clinical syndrome, morbidity, mortality, seasonal incidence, p. 248. II. A. Epidemic pattern. B. Outbreaks with distinctive features, p. 255.
17. György, P. and Goldblatt, H. Experimental production of dietary liver injury (necrosis, cirrhosis) in rats. *Proc. Soc. Exper. Biol. & Med.*, 46: 492, 1941.
18. Hanger, F. M. Serological differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsions. *J. Clin. Investigation*, 18: 261, 1939.
19. Havens, W. P., Jr. Infectious hepatitis. *Medicine*, 27: 279, 1948.
20. Havens, W. P., Jr. Report of a trip to Japan and Korea during the period 14 March–11 April 1951, to study viral hepatitis among American troops in these countries. (Unpublished.) Submitted to the Surgeon General, Department of the Army, April 25, 1951.
21. Himsworth, H. P. and Glynn, L. E. Massive hepatic necrosis and diffuse hepatic fibrosis (acute yellow atrophy and portal cirrhosis); their production by means of diet. *Clin. Sc.*, 5: 93, 1944.
22. Himsworth, H. P. Lectures on the Liver and Its Diseases, chapt. III, IV. Oxford, 1947. Basil Blackwell & Mott, Ltd.

23. Hoffbauer, F. W., Evans, G. T. and Watson, C. J. Cirrhosis of the liver; with particular reference to correlation of composite liver function studies with liver biopsy. *M. Clin. North America*, 29: 395, 1945.
24. Hoffbauer, F. W. Needle biopsy of the liver. *J. A. M. A.*, 134: 666, 1947.
25. Howard, R. and Watson, C. J. Antecedent jaundice in cirrhosis of the liver. *Arch. Int. Med.*, 80: 1, 1947.
26. Iversen, P. and Roholm, K. On aspiration biopsy of the liver with remarks on its diagnostic significance. *Acta med. Scandinav.*, 102: 119, 1939.
27. Kinsell, L., Weiss, H. A., Michaels, G. D., Shauer, J. S. and Barton, H. C. The correlation of hepatic structures and function. *Am. J. Med.*, 6: 292, 1949.
28. Klatskin, G. and Rappaport, E. M. Late residuals in presumably cured acute infectious hepatitis. *Ann. Int. Med.*, 26: 13, 1947.
29. Klatskin, G. and Yesner, R. Factors in the treatment of Laennec's cirrhosis of the liver. I. Clinical and histological changes observed during a period of bed rest, alcohol withdrawal, and a minimal basic diet. *J. Clin. Investigation*, 28: 723, 1949.
30. Klatskin, G. and Yesner, R. Hepatic manifestations of sarcoidosis and other granulomatous diseases. *Yale J. Biol. & Med.*, 23: 207, 1950.
31. Koszalka, M. F. Hepatitis and its sequelae, including development of portal cirrhosis. *Arch. Int. Med.*, 84: 782, 1949.
32. Krarup, N. B. and Roholm, K. The development of cirrhosis of the liver after acute hepatitis, elucidated by aspiration biopsy. *Acta med. Scandinav.*, 108: 306, 1941.
33. Kumpe, C. W., Gall, E. A., Schiff, L., Molle, W. E., Safdi, S. A. and Steinberg, H. W. Needle biopsy of the liver. General considerations. *Gastroenterology*, 9: 672, 1947.
34. Kunkel, H. G., Labby, D. H. and Hoagland, C. L. Chronic liver disease following infectious hepatitis: abnormal convalescence from initial attack. *Ann. Int. Med.*, 27: 202, 1947.
35. Lichtman, S. S. Hepatic insufficiency: pathophysiology and clinical aspects. *Ann. Int. Med.*, 25: 453, 1946.
36. Lucké, B. II. The structure of the liver after recovery from epidemic hepatitis. *Am. J. Path.*, 20: 595, 1945.
37. Maclagen, N. F. The thymol turbidity test as an indicator of liver dysfunction. *Brit. J. Exper. Path.*, 25: 234, 1944.
38. McMichael, J. Disease of the liver. A review of some clinical and biochemical problems as revealed by systematic biopsy studies. *J. A. M. A.*, 137: 234, 1948.
39. Mallory, T. B. Cirrhosis of the liver. Five different types of lesions from which it may arise. *Bull. Johns Hopkins Hosp.*, 22: 69, 1911.
40. Mallory, T. B. The pathology of epidemic hepatitis. *J. A. M. A.*, 134: 655, 1947.
41. Malloy, H. and Evelyn, K. A. The determination of bilirubin with the photoelectric colorimeter. *J. Biol. Chem.*, 119: 481, 1937.
42. Neefe, J. R. Results of hepatic tests in chronic hepatitis without jaundice: correlation with clinical course and liver biopsy findings. *Gastroenterology*, 7: 1, 1946.
43. Neefe, J. R., Stokes, J., Jr., Garber, R. S. and Gellis, S. S. Studies on the relation of the hepatitis virus to persistent symptoms, disability, and hepatic disturbance following acute infectious hepatitis. *J. Clin. Investigation*, 26: 329, 1947.
44. Popper, H. and Franklin, M. Diagnosis of hepatitis by histologic and functional methods. *J. A. M. A.*, 137: 230, 1948.
45. Popper, H., Steigmann, F., Meyer, K. A., Kozall, D. D. and Franklin, M. Correlation of liver function and liver structure. *Am. J. Med.*, 6: 278, 1949.
46. Popper, H., Steigmann, F. and Szanto, P. B. Quantitative correlation of morphologic liver changes and clinical tests. *Am. J. Clin. Path.*, 19: 710, 1949.
47. Roholm, K. and Iversen, P. Changes in the liver in acute epidemic hepatitis (catarrhal jaundice) based on 38 aspiration biopsies. *Acta path. et microbiol. Scandinav.*, 16: 427, 1939.
48. Schiff, L. The clinical value of needle biopsy of the liver. *Ann. Int. Med.*, 34: 948, 1951.
49. Sherlock, S. V. P. Aspiration liver biopsy: technique and diagnostic application. *Lancet*, 2: 397, 1945.
50. Sherlock, S. and Walshe, V. The post-hepatitis syndrome. *Lancet*, 2: 482, 1946.
51. Sherlock, S. Post-hepatitis cirrhosis. *Lancet*, 1: 817, 1948.
52. Volwiler, W. and Jones, C. M. The diagnostic and therapeutic value of liver biopsies with particular reference to trocar biopsy. *New England J. Med.*, 237: 651, 1947.
53. Volwiler, W. and Elliott, J. A. Late manifestations of epidemic infectious hepatitis. *Gastroenterology*, 10: 349, 1948.
54. Volwiler, W., Jones, C. M. and Mallory, T. B. Criteria for the measurement of results of treatment in fatty cirrhosis. *Gastroenterology*, 11: 164, 1948.
55. Watson, C. J. and Hoffbauer, F. W. The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver. *Ann. Int. Med.*, 25: 195, 1946.
56. Weisbrod, F. G., Schiff, L., Gall, E. A., Cleveland, F. P. and Berman, J. R. Needle biopsy of the liver. III. Experiences in the differential diagnosis of jaundice. *Gastroenterology*, 14: 56, 1950.

An Evaluation of Needle Biopsy of the Liver*

EDWARD R. CHRISTIAN, M.D.

New Orleans, Louisiana

THE large number of admissions to this hospital caused by diseases involving the liver have demanded for their proper management a tool with greater specificity than function tests to aid in establishing diagnoses, in determining the effects of treatment and in following the progress of disease processes. Biopsy was adopted to fill that need. At first specimens were obtained by laparotomy; however, disadvantages of the method precluded its practical application: (1) The suggestion of laparotomy alarmed many patients and refusals were frequent. (2) Patients in whom biopsy was most desirable were often so ill that the procedure significantly increased morbidity. (3) Trauma incident to exposing the liver induced parenchymal changes which simulated hepatitis. Consequently, that method was replaced by needle biopsy which has proved to be a most useful procedure with a gratifying degree of simplicity, efficiency and safety. These attributes have prompted the submission of this report as an encouragement for others to adopt the needle biopsy.

METHOD AND MATERIAL

A total of 104 biopsies were performed on ninety-one patients. Of the 104 one was a failure, one resulted in an inadequate specimen, one was destroyed in the staining process and one (done for culture purposes) followed an initial biopsy so closely that it was not counted. In the main part, therefore, the analysis includes 100 biopsies performed on eighty-nine patients. The group consisted of seventy white males, eighteen Negro males and one white female. All patients selected had historical, clinical or laboratory evidence of liver disease; not one was thought to have normal liver prior to biopsy.

Since needle biopsy affords the most satisfactory means of deriving benefit from serial examinations of liver tissue, each patient was approached as one in whom repeated biopsies were desirable. Care was taken to dispel preoperative apprehension, to make the procedure as painless as possible and to allay postoperative discomfort. Of the 104 biopsies sixty-three were done without preoperative sedation and forty-one were preceded by mild sedation, usually with small doses of meperidine hydrochloride (demerol). The favorable reputation of the procedure, established chiefly through patient-to-patient discussion, resulted in few refusals of the initial biopsy and in no refusal of subsequent biopsy.

The Vim-Silverman needle (3⅜ inch) was used in all biopsies. Ease of operation was facilitated by discarding the obturator and inserting the sleeve needle and split cannula as a unit. Without exception the site of needle insertion was in the right mid-axillary line in either the eighth or ninth intercostal space. The interspace which offered equal expanses of liver dullness caudad and cephalad was chosen. The eighth interspace was used in thirty-two biopsies; the ninth, in seventy-two biopsies. After infiltration of the tissues down to and including Glisson's capsule with 2 per cent procaine hydrochloride solution the proposed needle track was first explored with a spinal needle as a precaution against introduction of the larger biopsy needle into prohibitive structures such as large blood vessels, abscess cavities and adjacent viscera. Biopsy was then performed while the patient held his breath in expiration. Material thus obtained was studied by the Pathology Department of this hospital and then reviewed by the Armed Forces Institute of Pathology. Diagnoses referred to in

* From the Medical Service and Research Laboratory, Veterans Administration Hospital, New Orleans, and the Department of Medicine, The Tulane University of Louisiana School of Medicine, New Orleans, La. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration. This work was done in part under a contract between the Veterans Administration and Tulane University.

Figure 2 represent the joint opinions of those two groups.

RESULTS

Efficiency of the Vim-Silverman Needle. This instrument was found to be extremely simple to operate with the degree of speed required by the fact patients were not allowed to breathe during the biopsy procedure. The needle had the added advantage of causing so little discomfort that repeated attempts at biopsy could be made at the same site when the first resulted in an inadequate specimen. In our experience the Vim-Silverman needle has an over-all efficiency of more than 98 per cent as shown in Table I.

TABLE I
EFFICIENCY OF THE VIM-SILVERMAN NEEDLE IN LIVER BIOPSY

No. of Attempts at Biopsy	No. of Biopsies	No. Successful	No. of Failures
1	98	97	1 (Inadequate tissue)
2	5	4	1 (No tissue)
3	1	1	0
Totals	104	102	2
Per cent	...	98.1	1.9

Complications. Because biopsy of the liver by means of a needle entails puncture of a highly vascular organ without the aid of direct vision, hemorrhage and damage to adjacent viscera are the most feared complications in that order. Others to be considered include spreading of infection into the pleural and peritoneal cavities, damage to the lower lobe of the right lung and bile peritonitis resulting when the needle track opens a path for bile drainage. In this series complications were few and comparatively trivial. They are presented in Table II.

The forty-six patients who complained of pain included even those with minimal symptoms. The twenty-five patients requiring anodyne in most instances might have been managed without the use of drugs had we not been interested in establishing rapport to facilitate future biopsies. The patient who experienced nausea and vomiting was an aged white man who had undergone cholecystotomy years previously and was subject to recurrent episodes of upper abdominal distress. The patient in whom hemorrhage occurred was the only woman in the series. An uncooperative alcoholic, she got out of bed against orders and abdominal discomfort developed followed by evidence of bleeding the chief manifestations of which were pallor, fall in blood pressure and decrease in hematocrit. She was transfused with 1 pint of whole blood after which her condition stabilized and she had no further difficulty.

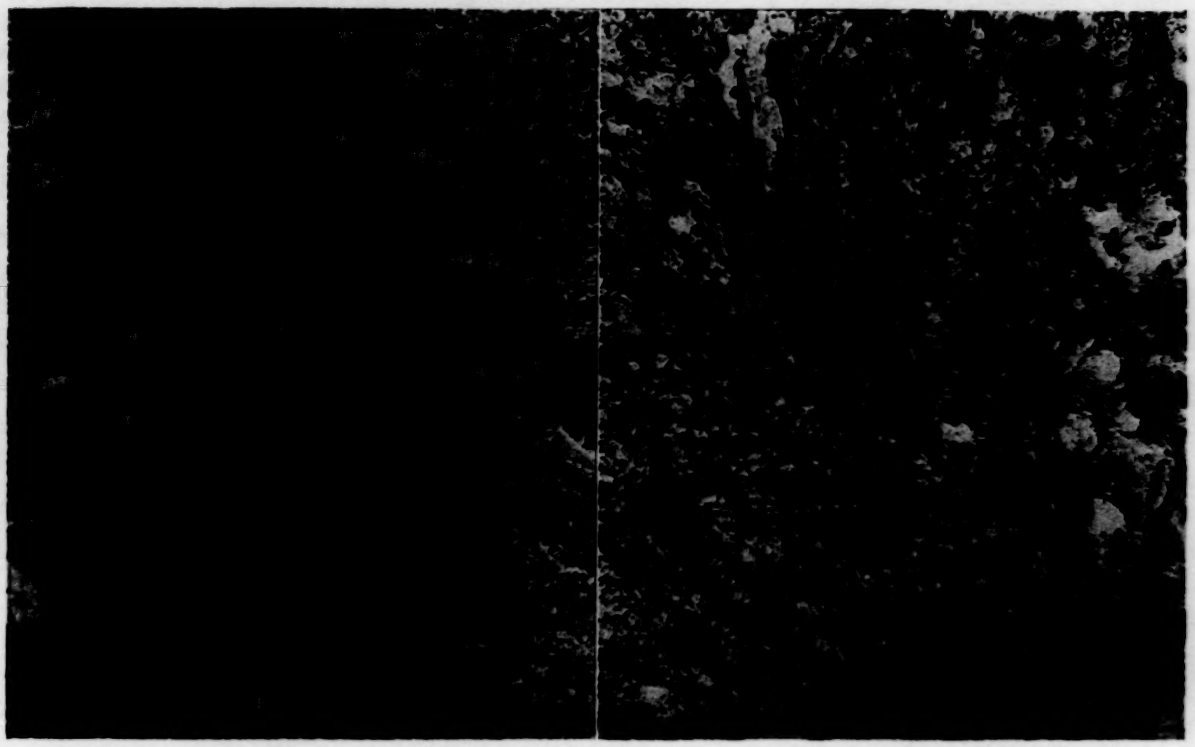
TABLE II
COMPLICATIONS OF NEEDLE BIOPSY OF LIVER

Complication		No. of Biopsies
Pain		46
Requiring anodyne	25	
Not requiring anodyne	21	
Nausea and vomiting		1
Hemorrhage		1

The infrequent occurrence of serious complications has made it possible to hospitalize subjects, biopsy and discharge them with safety in a period of twenty-four hours.

Effect of Needle Biopsy upon the Liver. In this series fourteen patients eventually died and underwent autopsy. In all but two the livers bore no evidence of the biopsy procedure. In one, who died several months after biopsy, there were numerous fibrous adhesions between the dome of the right lobe and the diaphragm. These were, probably, the result of undetected subcapsular hemorrhage following biopsy. The second patient died five days after biopsy from pulmonary embolus secondary to thrombophlebitis in a lower extremity. At autopsy serial sections were taken in the needle track which was still demonstrable. Figure 1A is a low power photomicrograph of one such section and reveals only minimal extravasation of blood. Figure 1B is a high power view of the same area and shows the invasion of numerous fibroblasts. These sections suggest that healing of the needle track is prompt and that delayed hemorrhage following biopsy is unlikely.

Diagnoses Established. For our own purposes needle biopsy of the liver has been of greatest value in helping to clarify differential diagnoses. The vast majority of patients admitted to this hospital are men and many of them are in the age group when neoplasms are frequent and the effects of prolonged dietary indiscretions become apparent. In that group biopsy has differentiated fatty metamorphosis from portal cirrhosis, thereby aiding in establishment of the plan for treatment. Not infrequently there have been patients in whom existence of neoplasms could not be ascertained however strongly sug-



1A 1B

FIG. 1. A, track of Vim-Silverman needle five days after biopsy showing minimal extravasation of blood (low power). B, high power view of the same area showing invasion of fibroblasts.

gested by clinical findings. In several such cases biopsy of the liver has demonstrated metastatic lesions thereby obviating exploratory surgery. Proof of metastatic liver disease, through its hopeless prognostic significance, has also served to preclude surgical intervention for questionable palliative effect. As the number of biopsies continues to mount, an increasing group of granulomatous lesions secondary to a variety of systemic diseases is being accumulated. Although not all such cases are reviewed in this report, the group to date includes brucellosis, tuberculosis, histoplasmosis, sarcoidosis, rheumatoid arthritis and non-specific granulomas in cases of fever of undetermined origin. Demonstration of hepatic granulomas has, on a few occasions, made possible accurate diagnoses in patients with pulmonary lesions, the exact nature of which could not be established by means of other evidence at hand.

The diagnoses established in this series of 100 needle biopsies of the liver are shown in Figure 2. Although hemosiderosis is listed as a separate diagnosis, it alone has not been regarded as evidence of abnormality except in two cases in which it was pronounced. Minor pigmentary changes such as lipofuscin deposits have not been listed among the pathologic findings, nor has evidence of regeneration.

Admission impressions were confirmed twenty-four times and corrected forty-nine times. Prebiopsy impressions were confirmed thirty-eight times and corrected thirty-five times. Diagnoses established by initial biopsies were affirmed by subsequent biopsies in seven cases. A total of fifteen biopsies were performed for investigational purposes as part of a research project; fourteen supplied additional information of value in the project and one did not. Of the 100 biopsies analyzed only two failed to substantiate established diagnoses and six failed to be of any value in establishing diagnoses.

Correlation of Biopsy Findings and Clinical Data. The chief function of needle biopsy of the liver is to establish an accurate diagnosis when that has not been possible through the use of clinical data. In this series abnormal liver tissue was demonstrated eighty-five times and normal tissue fifteen times. Figures 3, 4 and 5, respectively, compare complaints, physical findings and results of laboratory studies in those with abnormal tissue and those with normal tissue. Cursory review of the graphs emphasizes the fallacy in using such data as absolute criteria

for diagnosing liver disease. In selecting this group of patients, all of whom were thought to have abnormal liver tissue on the basis of clinical data, we were misled fifteen times.

CRITICISM OF NEEDLE BIOPSY

The most outstanding objection to needle biopsy is its inability to demonstrate isolated or widely separated hepatic lesions such as metastatic nodules, primary neoplasms, granulomas and focal areas of inflammation. This criticism is justified by the minute size of the specimen when compared with the entire organ and by the fact that it is obtainable from restricted areas without the aid of direct vision. It is thought that this short-coming of the procedure is far outweighed by its advantages. Moreover, the results of these 100 biopsies suggest that the objection is more theoretic than real. Specifically, fourteen patients subjected to biopsy subsequently went to autopsy. In only one case did the biopsy and autopsy findings fail to agree. In that particular case biopsy had been negative but autopsy seventy-nine days later revealed metastatic disease of the liver.

A brief study to determine the effectiveness of needle biopsy in representing the histology of the entire organ was undertaken. Ten deceased patients were selected at random; those with massive hepatic involvement, in whom needle biopsy would have demonstrated similar lesions regardless of site, were rejected. Each liver was "biopsied" with the Vim-Silverman needle in five widely separated areas, i.e., lateral aspect and dome of the right lobe, lateral aspect and dome of the left lobe and the caudate lobe. Specimens thus obtained were assigned secret identification and submitted to the pathologist for interpretation. As shown in Figure 6 there was general agreement between findings in the specimens obtained by needle and those established by thorough examination of the entire organ.

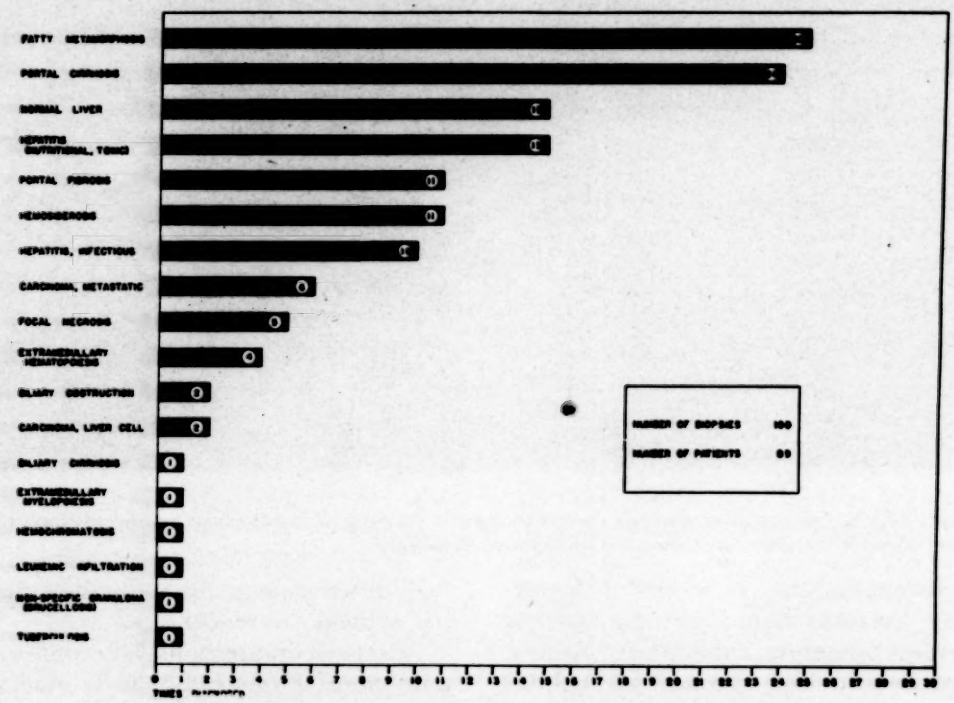


FIG. 2. Frequency of diagnoses established by needle biopsy of liver.

Another objection to needle biopsy is that specimens so obtained are too small for adequate histologic studies. To the contrary, we have found the specimens obtained by the Vim-Silverman needle to be of sufficient quantity to allow routinely several staining procedures. General architecture has been demonstrated by hematoxylin-eosin, tri-chrome and azocarmine preparations. Chemical composition has been demonstrated by the Gömöri technic for alkaline phosphatase, Best's carmine and Hotchkiss technics for polysaccharides, Turnbull's blue stain for hemosiderin and Sudan black and oil red stains for fat. Thus a single specimen can supply forty-five to sixty micro-

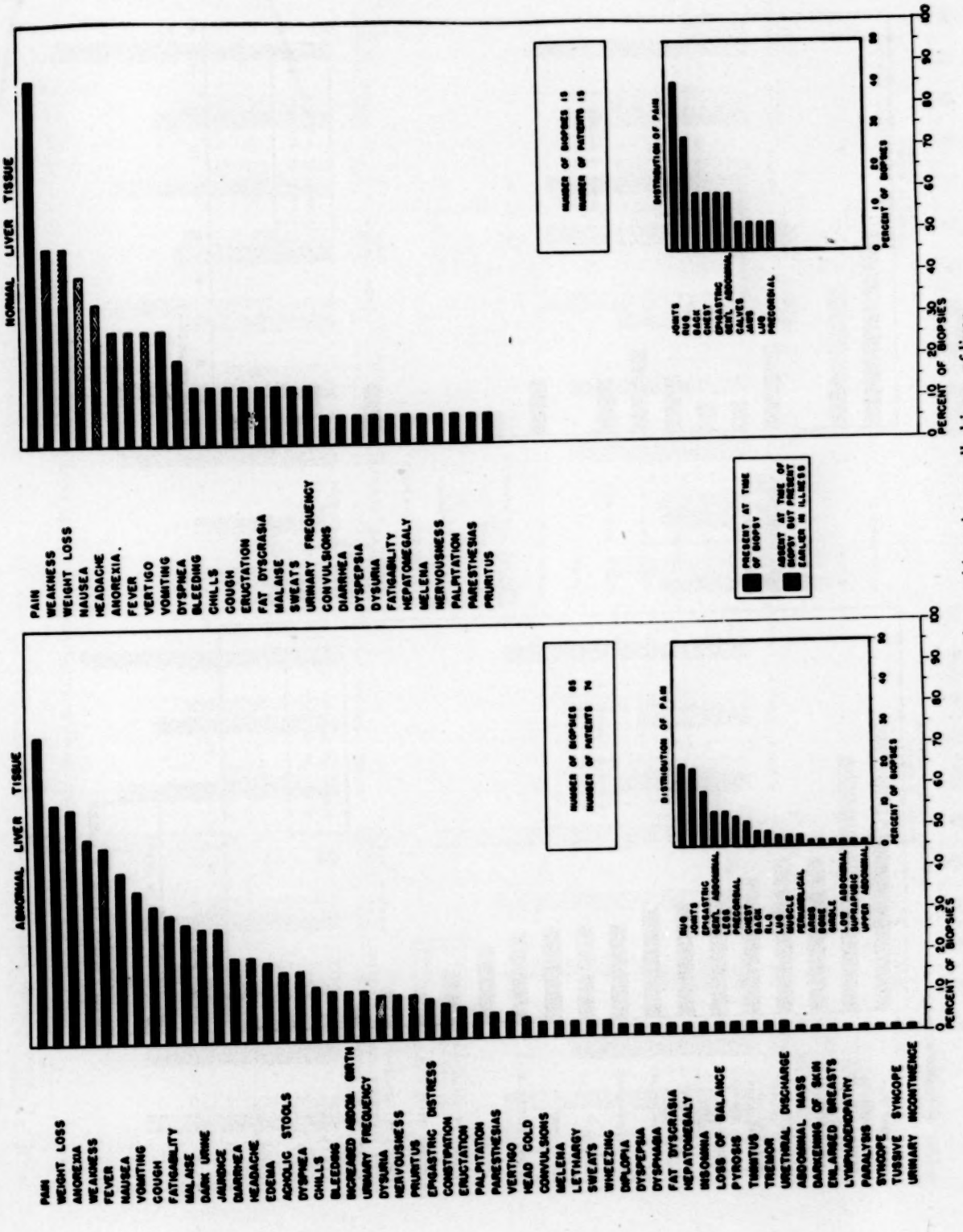


FIG. 3. Complaints of patients later subjected to needle biopsy of liver.

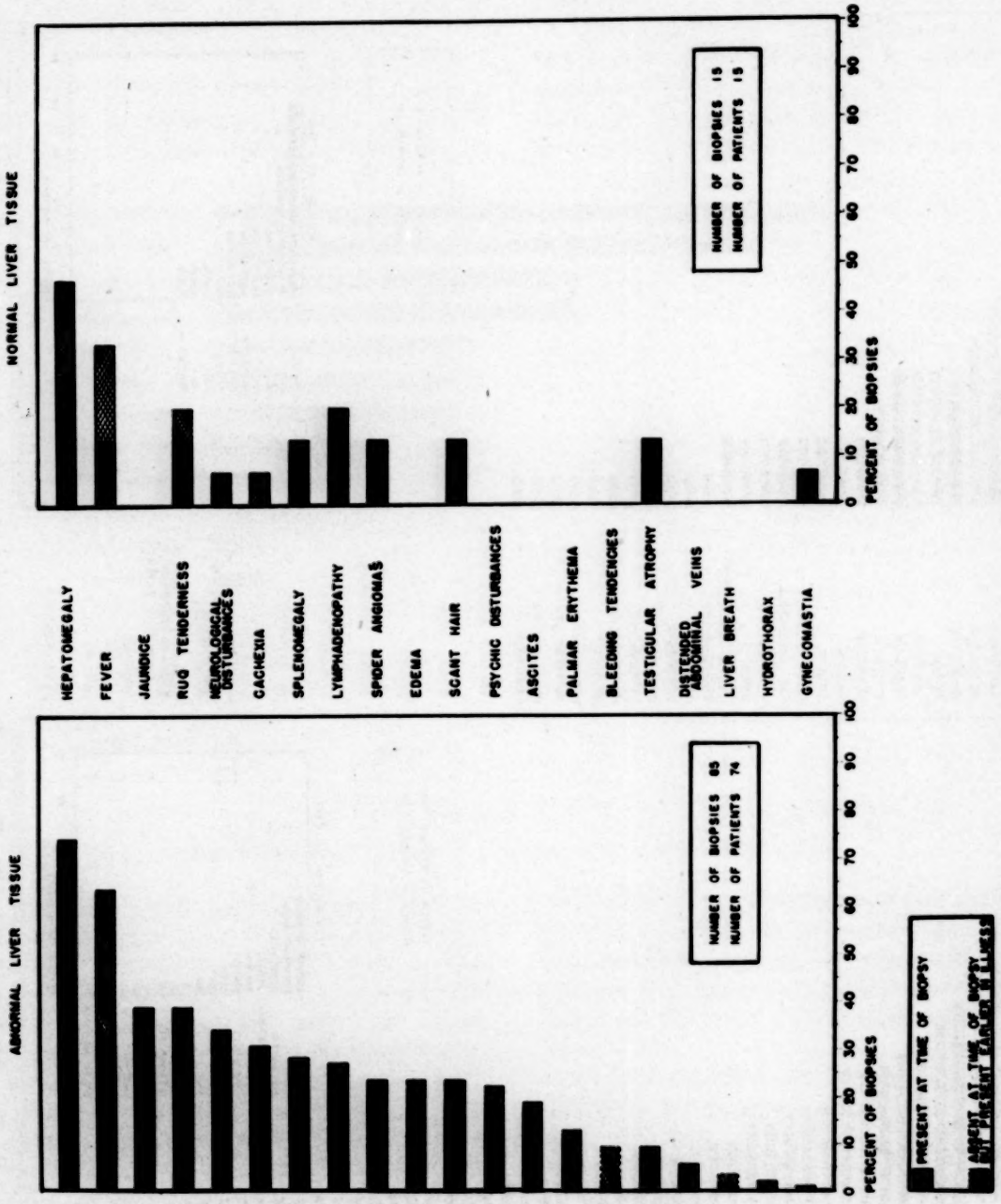


FIG. 4. Physical findings in patients subjected to needle biopsy of liver.

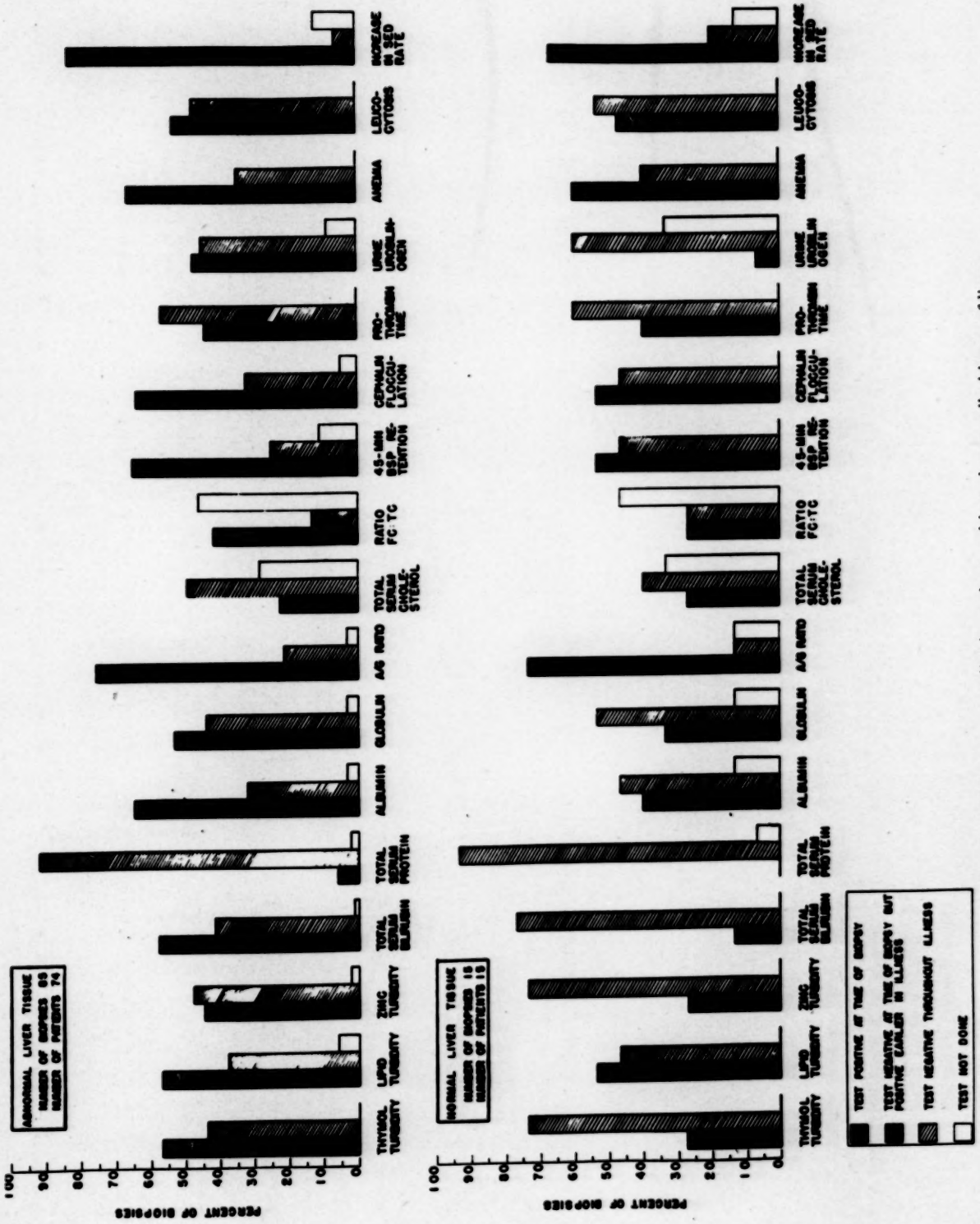


FIG. 5. Results of laboratory studies in patients subjected to needle biopsy of liver.

SITES OF NEEDLE ENTRY →					LATERAL ASPECT OF THE RIGHT LOBE	LATERAL ASPECT OF THE LEFT LOBE	DOME OF THE RIGHT LOBE	DOME OF THE LEFT LOBE	CAUDATE LOBE	OVERALL DIAGNOSES ESTABLISHED BY AUTOPSY	LIVER PATHOLOGY ESTABLISHED BY AUTOPSY
CASE	RACE	SEX	AGE	HOURS PM							
19027	W	M	61	7	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL; SOME BILE PIGMENT OR HEMOSIDERIN	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL; SOME BILE PIGMENT OR HEMOSIDERIN	ESSENTIALLY NORMAL; SOME BILE PIGMENT OR HEMOSIDERIN	ASHOGENIC MYELOID METAPLASIA	EXTRAMEDULLARY MYELOPOIESIS; HEMOSIDEROSIS
16165	W	M	31	7	POST-MORTEM NECROSIS; BILE THROMBI; LIPOFUSCIN	POST-MORTEM NECROSIS	POST-MORTEM NECROSIS	POST-MORTEM NECROSIS	POST-MORTEM NECROSIS; BILE THROMBI	DIFFUSE COLLAGEN DISEASE	CHRONIC PASSIVE CONGESTION
19326	N	M	52	24	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	BRONCHOGENIC CARCINOMA	CHRONIC PASSIVE CONGESTION
21431	W	M	60	13	MALIGNANCY, UNDIFFERENTIATED SUGGESTING LYMPHOMA	ESSENTIALLY NORMAL; POST-MORTEM CHANGE	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL; POST-MORTEM CHANGE	POST-MORTEM NECROSIS	RETICULUM CELL LYMPHOSARCOMA	METASTATIC LYMPHOSARCOMA
22207	W	M	38	8	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL; SEPSIS	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL; SEPSIS	BRONCHOGENIC CARCINOMA	CHRONIC PASSIVE CONGESTION
22256	N	M	39	3	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL, SEPSIS	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL; CENTROLOBULAR NECROSIS POSTMORTEM	ESSENTIALLY NORMAL	PYELONEPHRITIS WITH SEPTICEMIA	TOXIC HEPATITIS
22610	W	M	50	12	ESSENTIALLY NORMAL; MILD REDEGRATION	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL; SEPSIS	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	ARTERIOSCLEROTIC HEART DISEASE	CHRONIC PASSIVE CONGESTION
22737	W	M	60	10	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	ESSENTIALLY NORMAL	DIABETES MELLITUS; BRONCHOPNEUMONIA	CHRONIC PASSIVE CONGESTION
22978	W	M	61	9	CENTRAL DEGENERATION (AGONAL)	CENTROLOBULAR DEGENERATION (POST-MORTEM)	CENTROLOBULAR NECROSIS (HEART FAILURE)	ESSENTIALLY NORMAL; POST-MORTEM CHANGE	POST-MORTEM NECROSIS; CONGESTION	ARTERIOSCLEROTIC HEART DISEASE	CHRONIC PASSIVE CONGESTION
23774	W	M	28	2	ESSENTIALLY NORMAL; POST-MORTEM DEGENERATION	CENTROLOBULAR NECROSIS (POST-MORTEM)	ESSENTIALLY NORMAL; SLIGHT POST-MORTEM NECROSIS	POST-MORTEM NECROSIS	ESSENTIALLY NORMAL	RHEUMATIC MYOCARDITIS AND MITRAL VALVULITIS	CONGESTION

FIG. 6. Comparison of findings in tissue obtained by scattered postmortem needle "biopsies" with those established by autopsy.

scopic sections for at least nine staining procedures. Furthermore, a portion of the specimen can be reserved for culture purposes when indicated. Specimens obtained by the Vim-Silverman needle withstand the aforementioned technics, one of which involves freezing, without undergoing fragmentation.

CASE REPORTS

CASE I. The patient (No. 21807), a twenty-seven year old white male shipping clerk, was hospitalized because of pain in the right upper quadrant of the abdomen. The symptom was first noticed fifteen months prior to admission and prompted a visit to the family physician who discovered an enlarged liver and Endamoeba histolytica in his stool. He was given a course of amebicidal therapy but the pain persisted as his only complaint. The youth remained well enough to participate in sports. Past history revealed that he had been confined to bed for three weeks when he was seven years old by an episode of jaundice.

Physical examination revealed a robust individual weighing 222 pounds and appearing in the best of health. The only noteworthy finding was hepatomegaly, the smooth nontender liver extending about 5 inches below the right costal margin.

Laboratory studies were inconclusive. Hemogram revealed a total leukocyte count of 11,850 per mm.^{3}; differential was normal with exception of 4 per cent eosinophils; hemoglobin was 13.5 gm. per cent. Bromsulphalein retention at forty-five minutes was 18 per cent. Total serum cholesterol was 243 mg. per cent; free cholesterol, 96 mg. per cent; ratio of free cholesterol to total, 40 per cent. Numerous other blood studies and hepatic function tests were within normal limits. Stool examinations for parasites and complement fixation for amebiasis were negative. Barium enema revealed a lesion in the mid-descending colon which had the appearance of an inflammatory, granulomatous lesion; however, the possibility of a neoplasm could not be excluded.

Because the exact nature of the colonic lesion was not known, needle biopsy of the liver was performed and revealed metastatic adenocarcinoma. (Fig. 7.) The patient was then subjected to resection of the primary lesion to prevent impending obstruction. Fortunately, an end-to-end anastomosis was possible. Recovery from surgery was uneventful and the patient lived a comparatively comfortable and active life until he died in liver failure five months thereafter.

CASE II. The patient (No. 22086) was a forty-three year old Negro man admitted with complaints of tightness across the upper abdomen, night sweats, fatigability and weight loss. Symptoms had been present for three months. During that period appetite had remained excellent and there had been no nausea, vomiting or change in bowel habits. Years previously he had been told that he was "phthisic" as a child. He had malaria as an adult and had been in the South Pacific for twenty-nine months during World War II.

Physical examination revealed a well developed, rather poorly nourished individual who appeared chronically ill. His temperature was 104°F. A blowing systolic murmur was audible over the entire precordium. The liver was generally enlarged and slightly tender; it extended about 5 inches below the costal margins. The major portion of the entire left half of the abdomen was occupied by the slightly tender spleen.

Laboratory studies were of no aid in establishing a diagnosis. Briefly, hemogram revealed panhematocytopenia and liver function tests were compatible with diffuse parenchymal damage. Initial x-ray of the chest was negative. Numerous examinations of sputum and gastric washings were negative for acid-fast bacilli.

Diagnoses considered included lymphoma, Banti's syndrome, cirrhosis with hepatoma, sarcoidosis, tuberculosis and histoplasmosis. Needle biopsy of the liver was performed and revealed granulomatous hepatitis. One granuloma appeared to be a typical tubercle complete with Langhans' giant cells. (Fig. 8.) On the basis of that a diagnosis of miliary tuberculosis was made. Culture of the biopsy specimen for Mycobacterium tuberculosis was sterile. The patient was treated with streptomycin and made a dramatic response. His temperature, which had been spiking daily to 103°–105°F., returned to normal by lysis; the spleen and liver diminished in size and there was considerable improvement in liver function tests. Eventually lesions suggesting tuberculous involvement were demonstrated in some vertebrae and, questionably, in one lung. It was thought that the massively involved spleen was serving as a reservoir of infection and the patient was subjected to splenectomy. He died following

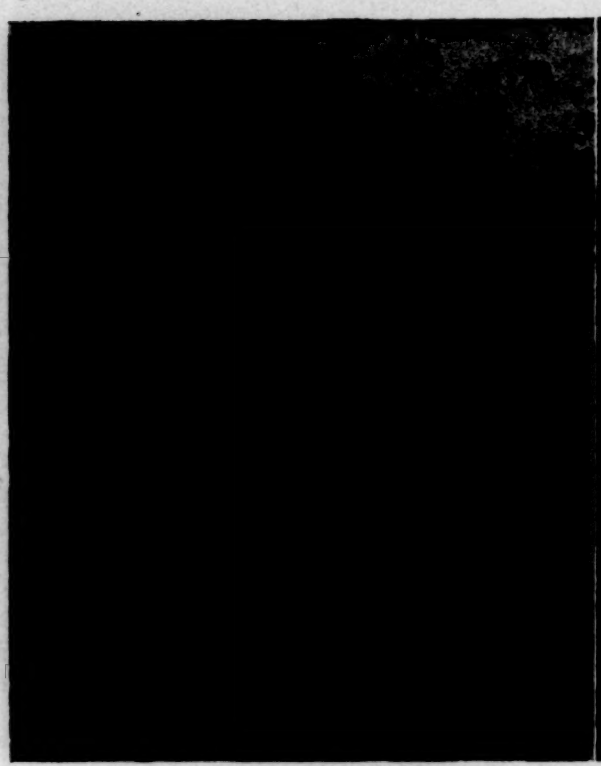


FIG. 7. Metastatic adenocarcinoma.

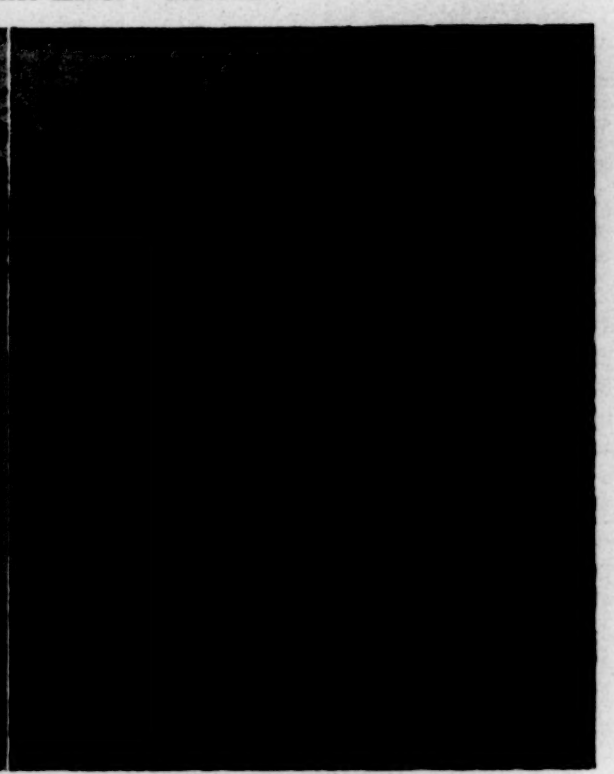
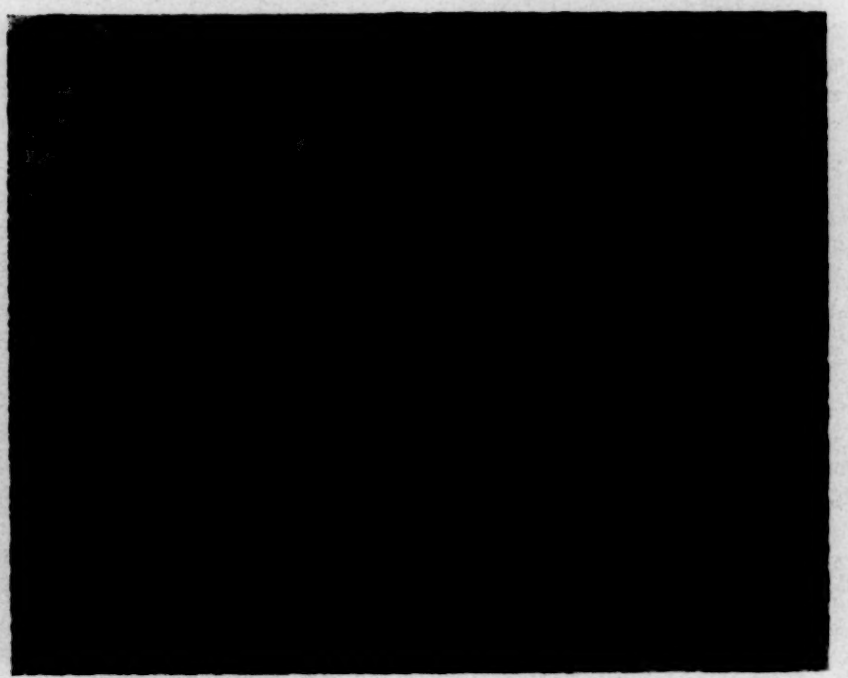


FIG. 8. Miliary tuberculosis.



9A 9B

FIG. 9. A, portal cirrhosis before treatment and B after treatment.

postoperative hemorrhage. Autopsy, confined to the abdomen, revealed extensive tuberculosis of the spleen, liver and lymph nodes.

Case III. The patient (No. 18555), a 32-year-old Negro man, was hospitalized with chief complaints of nausea, vomiting and cramping lower abdominal pain; symptoms had been present for six hours. For a month prior to admission he had been aware of anorexia, dysuria, urinary frequency and reddish discoloration of his urine. He had been drinking several pints of wine daily to the exclusion of adequate food. During a previous period of hospitalization a diagnosis of schizophrenia had been established.

Physical examination revealed a well developed, poorly nourished individual who appeared acutely ill and on the brink of coma. His temperature was 104°F.; evidence of dehydrations and malnutrition was pronounced. The smooth, slightly tender liver extended about 5 inches below the right costal margin. A few ecchymotic areas were present in one antecubital space.

Initial hemogram revealed a normal total leukocyte count and differential; hemoglobin was 10.5 gm. per cent. There was 3 plus albuminuria; pyuria was marked and a few erythrocytes were present in each high power field. Blood urea nitrogen was 60 mg. per cent; plasma bicarbonate content was 9 mEq./L. Total serum protein was 5.6 gm. per cent with 2.4 gm. per cent albumin and 3.2 gm. per cent globulin. Total serum bilirubin was 8.1 mg. per cent; thymol turbidity was 9 units. Other liver function tests were within normal limits. X-ray of the chest was negative. Electrocardiogram revealed diffuse ischemia.

A definite diagnosis could not be established with ease. Jaundice combined with mental symptoms and evidence of cardiorenal involvement suggested Weil's disease. Progressive anemia, jaundice and reticulocytosis (which reached 10 per cent) suggested a hemolytic process. Evidence of marked toxicity, high fever, hepatomegaly and increasing leukocytosis (the total count reached 20,000 per mm.^{3}) suggested liver abscess. Needle biopsy of the liver was performed and revealed portal cirrhosis with fatty metamorphosis. (Fig. 9A.) Urine cultures grew Escherichia coli. The patient responded promptly to a regimen which included bed rest, parenteral fluids, full liver support and streptomycin for pyelonephritis. The liver diminished

Fig. 10. Fatty metamorphosis (Sudan black).

in size, jaundice subsided and other hepatic function tests improved. Liver biopsy was repeated six weeks after the first and showed improvement. (Fig. 9B.)

Case IV. The patient (No. 23396) was a fifty-five year old business man hospitalized because of angina pectoris and fatigability. Symptoms had been present for two years and were gradually becoming worse. He also complained of postprandial epigastric pain and belching relieved by antacids and low fat diet. During a period of hospitalization two years previously a diagnosis of arteriosclerotic heart disease had been established. In 1942 the patient had an episode of jaundice following immunization for yellow fever. Over a fifteen-year period he had been accustomed to drinking several highballs daily but, allegedly, had discontinued the practice.

Physical examination revealed a well developed individual weighing 165 pounds who did not appear ill. Other than palmar erythema there was no noteworthy finding.

Significant laboratory studies were restricted to hepatic function tests. Fasting serum lipid turbidity was 2,640 mg. per cent. Total serum cholesterol was 188 mg. per cent; free cholesterol, 81 mg. per cent; ratio of free cholesterol to total, 43 per cent. Stools contained increased

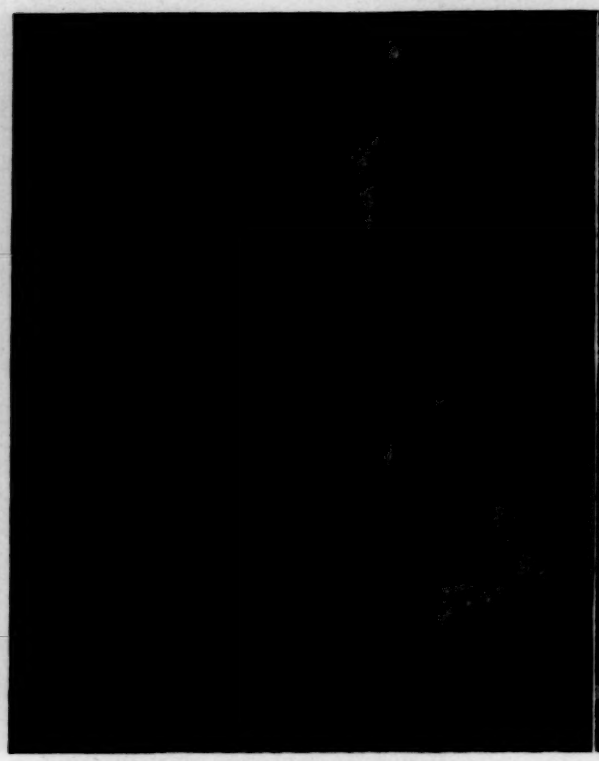


FIG. 11. Histoplasma capsulatum.

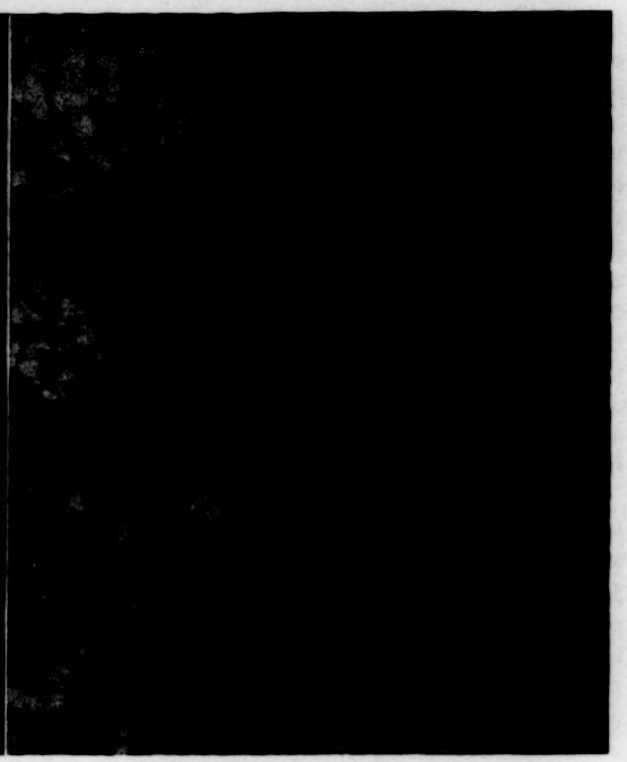


FIG. 12. Granuloma in sarcoidosis.

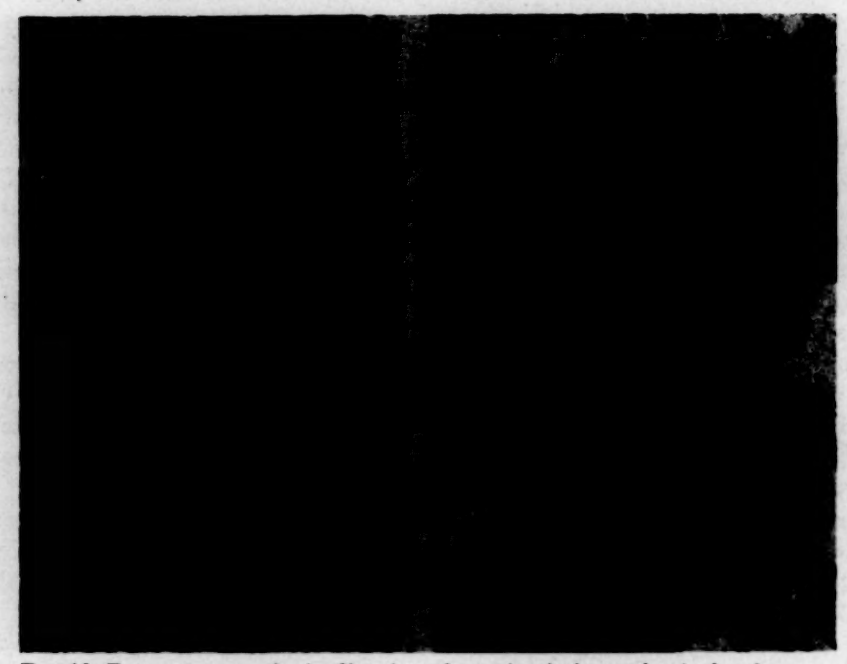
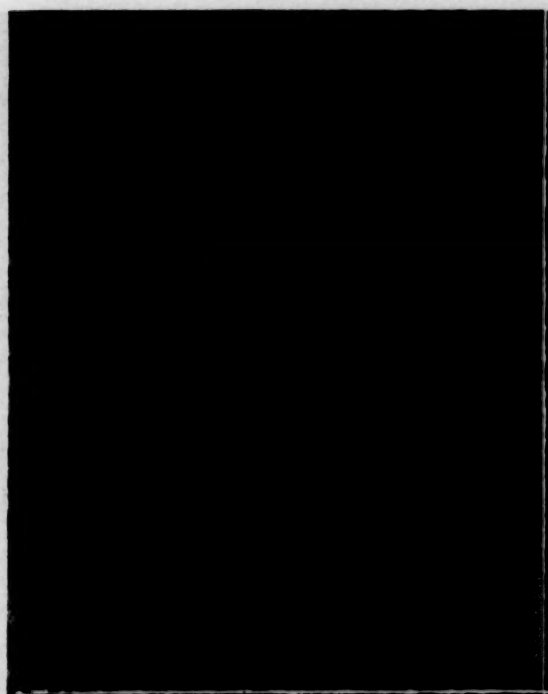
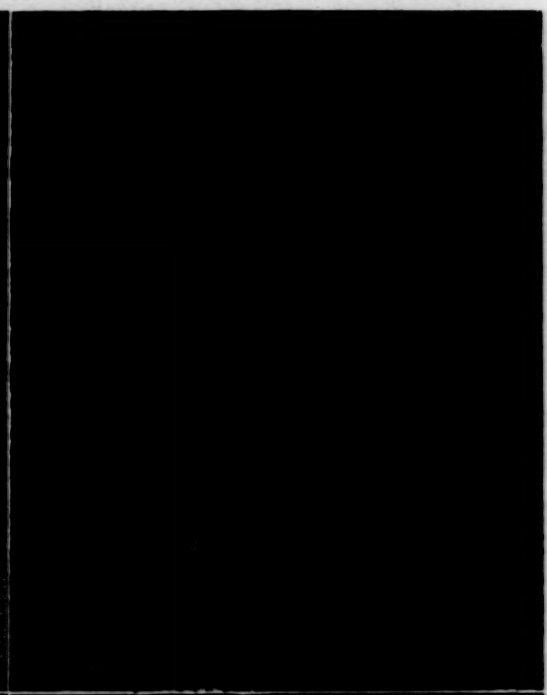


FIG. 13. Fatty metamorphosis, fibrosis and scarring in hepatolenticular degeneration.

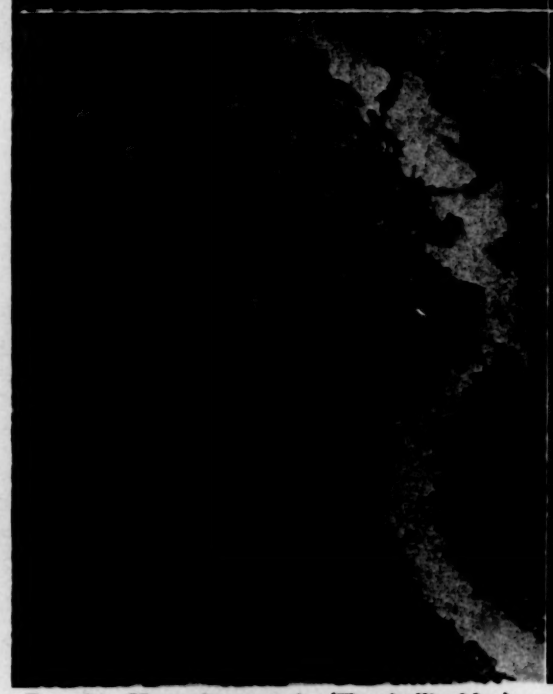
14



15



16



17

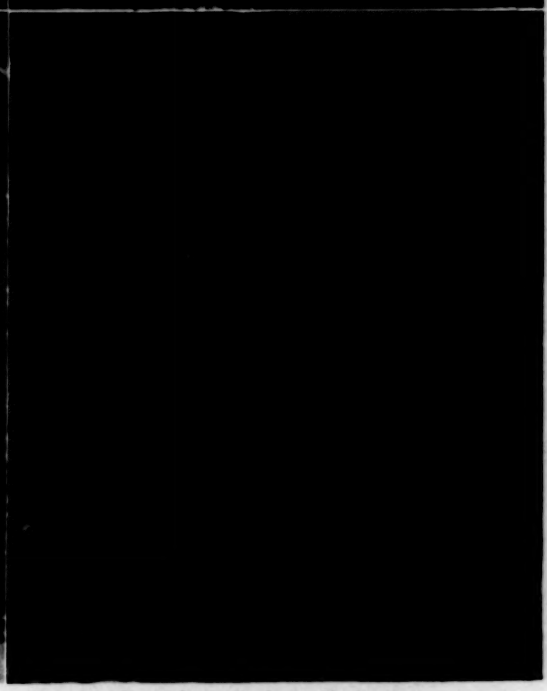


FIG. 14. Hemochromatosis (Turnbull's blue).

FIG. 15. Granuloma in brucellosis.

FIG. 16. Focal inflammatory lesion in amebic hepatitis.

FIG. 17. Fibrin thrombus; portal vein occluded by neoplasm.

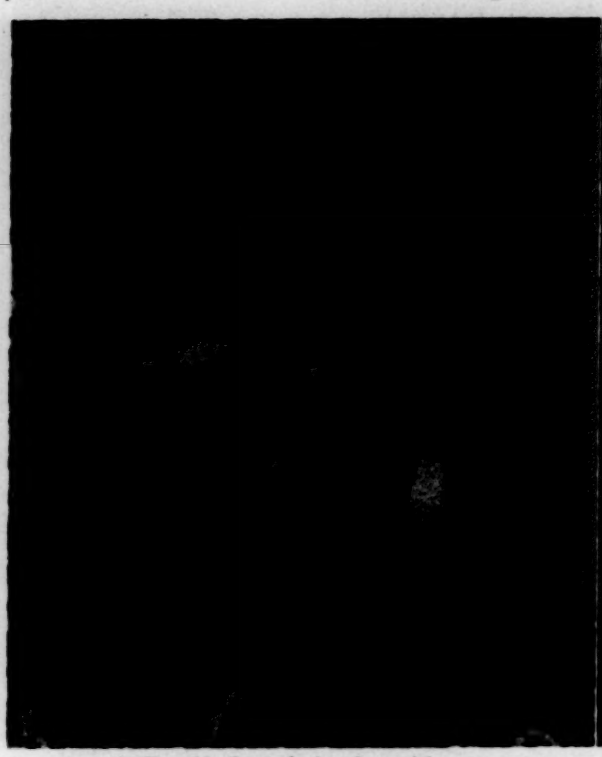


FIG. 18. Inoculation hepatitis.

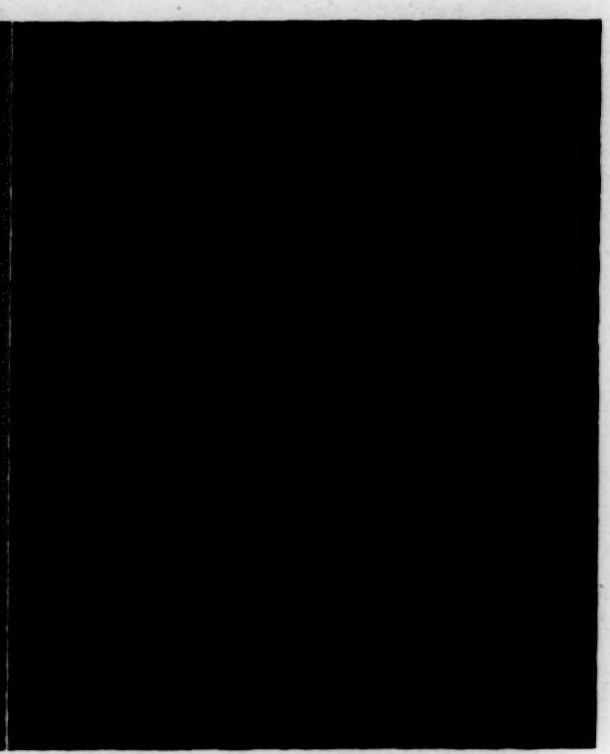


FIG. 19. Bile thrombi in biliary obstruction.

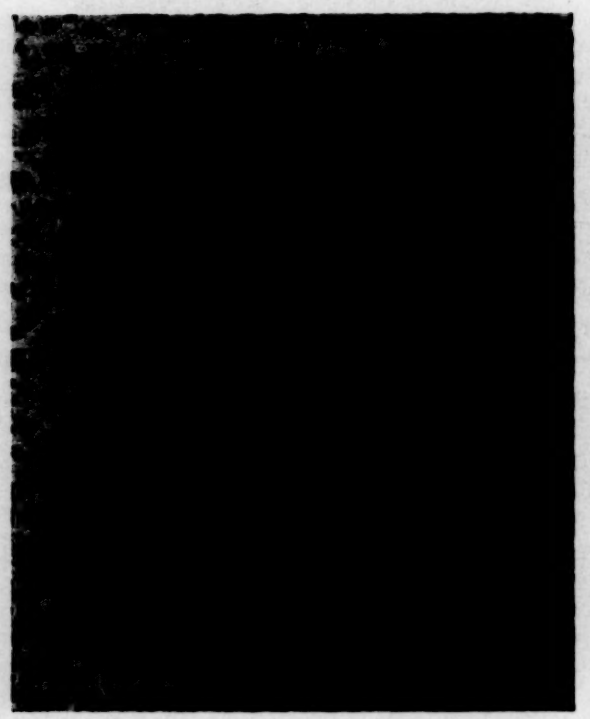


FIG. 20. Granuloma in fever of undetermined origin.

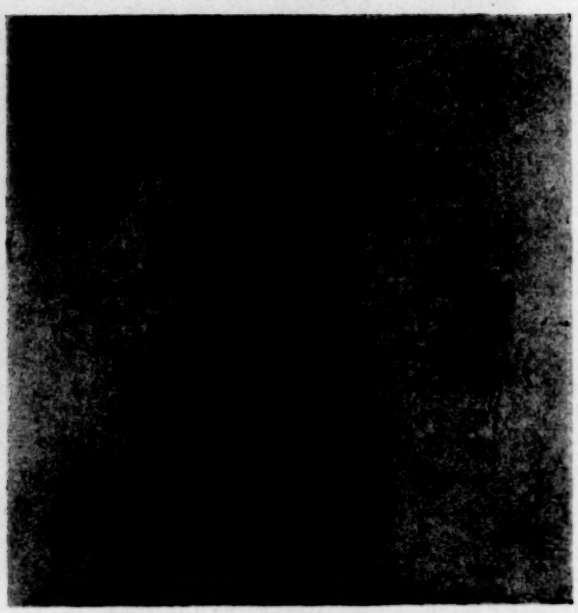


FIG. 21. Extreme nodularity in portal cirrhosis (low power view of entire biopsy specimen).

fat globules and calcium soaps. Fecal urobilinogen was 221 mg. in twenty-four hours. Electrocardiogram revealed diffuse ischemia. Gastrointestinal series suggested a small hiatal hernia and duodenitis. Gallbladder visualization was normal. Gastric analysis revealed moderate hyperacidity; duodenal drainage was negative. Basic metabolic rate was minus 3 on one occasion and minus 6 on another.

After hyperlipemia had been demonstrated by laboratory studies, consideration was given to its cause and possible effect on the patient's coronary atherosclerosis and resultant anginal attacks. Needle biopsy of the liver was performed and revealed marked fatty metamorphosis. (Fig. 10.) The patient was then placed on a low fat diet supplemented with choline. When discharged six weeks later he had not enjoyed appreciable change in his anginal attacks; however, his fasting serum lipid had decreased from 2,640 to 830 mg. per cent.

Figures 11 to 22 embody a collection of photomicrographs of various lesions demonstrated by needle biopsy of the liver. The frequency of liver disease necessitating biopsy for complete study is emphasized by the fact that these lesions and many others not illustrated were collected over the brief period of eighteen months. A few of the lesions shown are from cases not included in the text of this paper.

FIG. 22. Leukemia.

CONCLUSIONS

1. Needle biopsy is a practical adjunctive procedure in the diagnosis and management of liver disease.

2. Its use is warranted by the frequent inadequacy of clinical and laboratory data in fully delineating liver disease.

3. When performed in the hospital with sensible precautions it is virtually free from serious complication.

4. The Vim-Silverman needle is simple to operate and has an efficiency of more than 98 per cent in obtaining adequate tissue specimens.

5. Needle biopsy obviously cannot always demonstrate histology of the entire organ; however, its failure to do so appears to be infrequent.

6. Biopsy specimens obtained by the Vim-Silverman needle are of sufficient quantity and sturdiness to allow numerous staining technics.

SUMMARY

The results of 100 needle biopsies of the liver accomplished with the Vim-Silverman needle are reviewed. Lack of correlation between histologic findings and clinical data is demonstrated graphically. Criticism of the needle biopsy is discussed. Case histories illustrating practical application of the procedure and photomicrographs of various lesions demonstrated by it are presented.

Acknowledgment: Gratitude is expressed to Dr. Joseph Ziskind for his interpretation of tissue preparations and to Mrs. Shirley Fairchild, M.T., Miss Regina Noel, M.T., and Miss Billie Boulware, R.N., for their technical assistance. Photographic work was done by Mr. F. W. Busic and Mr. W. D. Bohon.

Altered Liver Function of Chronic Congestive Heart Failure*

JOHN M. EVANS, M.D., HYMAN J. ZIMMERMAN, M.D., J. GRANT WILMER, M.D., LAWRENCE J. THOMAS, M.D. *and* CLAYTON B. ETHRIDGE, M.D.

Washington, D. C.

CHRONIC congestive heart failure is characterized by widespread, complex and interrelated changes in various functions of the human body. That the liver is involved in these changes has been shown by numerous anatomic and physiologic studies.[1–10] There is, however, little agreement among investigators as to the basic mechanisms producing the hepatic alterations. Anoxia, venous hypertension, malnutrition and infection, acting singly or in combination, have all been suggested as factors in the pathogenesis of the process. The possibility that the hepatic disturbance may secondarily modify the heart failure state remains a matter for speculation.

In an attempt to appraise responsible mechanisms and possible functional interrelationships between the liver and the cardiocirculatory system, in patients with chronic congestive heart failure, a series of studies has been undertaken. The present report considers the nature and severity of liver impairment in the presence of cardiac decompensation and as compensation is restored. It also provides information concerning the role of venous pressure and arterial or hepatic hypoxia in determining or influencing the hepatic impairment.

MATERIALS AND METHODS

The patients studied were from two sources: Group I from the wards and outpatient service of The George Washington University Hospital; Group II, hospitalized patients from the Gallinger Municipal Hospital. Most of the hospitalized patients were studied shortly after admission and some were re-examined serially as compensation was restored. In a few instances observations have been repeated in the outpatient clinic over a period of months. Only in cases in which the existence of heart failure was unequivocal have the data been included. The criteria for congestive heart failure were those of The New York Heart Association.[11] Subjects have been excluded with proven or suspected primary liver disease, pulmonary infection, diabetes mellitus, hyperthyroidism, severe anemia, carcinomatosis or pulmonary infarction.

From seventy-three patients in Group I fifty-six were found to conform to the criteria for unequivocal heart failure in the absence of the complicating conditions enumerated previously. In Group II there were more than 100 patients with evidence of heart failure in whom liver function studies were performed. Forty-nine of these were found to meet the requirements for admission to the series. The 105 patients thus selected provide the basis for this report. Serial studies, as compensation was restored, were available in thirty patients.

The liver function tests were performed with the patient in the fasting state for from six to twelve hours. At the same time the venous pressure was measured according to the method of Lyons and Burwell[12] and a sample of arterial blood was obtained for determination of the oxygen saturation by the method of Van Slyke and Neill.[13] In Group II in some instances the venous pressure was obtained either the day before or the day after the liver studies.

The studies of liver function included bromsulfalein excretion, thymol turbidity, cephalin-cholesterol flocculation, serum bilirubin, and determination of serum albumin and globulin. The bromsulfalein test was performed according to Mateer's modification,[14] using the 5 mg. per

* From the Department of Medicine, The George Washington University Medical School, Washington, D. C. This work was supported by a research grant from The National Heart Institute, National Institutes of Health, United States Public Health Service.

kg. dose. The degree of dye retention was determined spectrophotometrically in a sample taken at forty-five minutes with retention of 5 per cent or more regarded as abnormal. The thymol turbidity test was done by Maclagan's method[15] using the modification of Shank and Hoagland[16] for the spectrophotometer.* The upper limit of normal was considered to be four units. The cephalin-cholesterol flocculation test was carried out according to Neefe's modification[17] of the procedure of Hanger[18] with a reading of 3 or 4 plus at forty-eight hours considered positive. The serum bilirubin level was determined by Malloy and Evelyn's[19] modification of the Van den Bergh method with 1.0 mg. per cent the upper limit of normal. The albumin and globulin levels were estimated by the method of Cohn and Wolfson[20] who indicate a normal range of 6.3 to 8.0 gm. per cent for total protein; 3.9 to 5.3 for albumin and 1.3 to 3.0 for globulin. In four patients hepatic vein catheterization was carried out in accordance with the procedure outlined by Dexter and associates.[21]

RESULTS AND COMMENT

The etiologic diagnosis of the 105 patients in both groups is listed in Table I. Information concerning the duration of heart failure is incomplete. However, with few exceptions these patients had evidence of cardiac decompensation for at least one month and in the majority the process was long-standing and recurrent.

Table II shows the incidence of abnormality of liver function by the tests employed in the entire group at the initial study. Of the 103 patients whose studies included the bromsulfalein excretion test, all showed impaired excretion of the dye except four in whom the degree of cardiac decompensation was minimal. Figure 1 presents the data on bromsulfalein excretion graphically and indicates the retention found at the initial study in each instance. Since the tests were usually performed shortly after admission the results reflect the height of the hepatic functional impairment in most instances. Generally speaking, but with a few exceptions, the degree of bromsulfalein retention corresponded to the severity of the congestive failure.

Table III shows the relationship of the excretion of bromsulfalein to the response to treatment. Of the thirty patients studied serially during hospitalization all but seven showed

TABLE I
ETIOLOGIC DIAGNOSIS OF THE HEART DISEASE IN THE 105 PATIENTS STUDIED

Etiologic Diagnosis	Group I	Group II	Total
Arteriosclerotic	20	13	33
Hypertensive	10	23	33
Rheumatic	12	8	20
Syphilitic	4	1	5
Pericardial effusion etiology unproven	5	0	5
Congenital, acyanotic	2	1	3
Cor pulmonale	0	2	2
Undetermined	3	1	4
Total	56	49	105

TABLE II
INCIDENCE OF ABNORMALITY OF LIVER FUNCTION IN 105 PATIENTS WITH CONGESTIVE FAILURE

Liver Function Test	Group I			Group II			Total		
	Performed (No.)	Abnormal		Performed (No.)	Abnormal		Performed (No.)	Abnormal	
		(No.)	(%)		(No.)	(%)		(No.)	(%)
Bromsulfalein	55	51	92.7	48	48	100	103	99	96.1
Thymol turbidity	49	20	40.8	44	14	31.8	93	34	36.5
Cephalin flocculation	40	7	17.5	48	17	35.4	88	24	27.2
Serum bilirubin	53	14	26.4	0	0	0	53	14	26.4

* The Coleman Junior model spectrophotometer was employed throughout.

improvement in dye excretion. The twenty-three patients with improved bromsulfalein excretion had good response to treatment for congestive failure as measured by the usual criteria. In six of the seven patients with no improvement in liver function the heart failure was refractory or partially refractory to treatment; in one patient with a good therapeutic response there was no apparent reason for the continued dye retention. The mean of the bromsulfalein retention after treatment was 9 per cent, varying from less than 5 per cent to 26 per cent.

Figure 2 presents the relationship between the percentage of dye retention and the percentage of arterial oxygen saturation. It is apparent that there is a poor correlation between the bromsulfalein retention and the arterial oxygen values. On the other hand, as shown in Figure 3, retention of the dye seems to correlate well with the level of venous pressure.

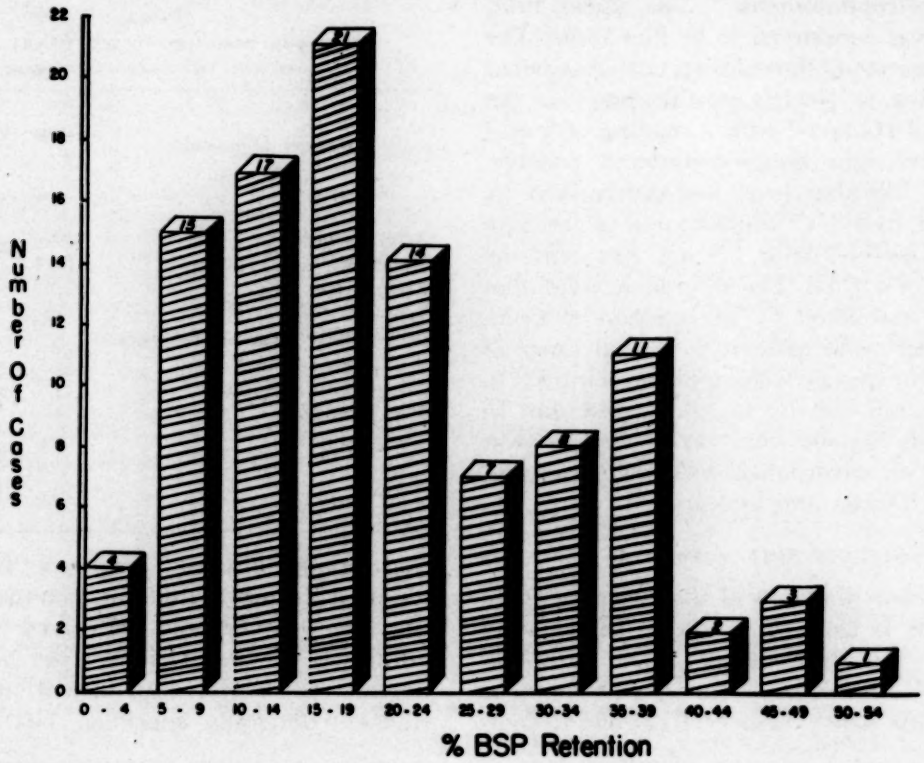


FIG. 1. The percentage of bromsulfalein retention in 103 patients with congestive heart failure.

TABLE III
IMPROVEMENT IN BROMSULFALEIN EXCRETION AS RELATED TO RESPONSE TO THERAPY FOR CONGESTIVE HEART FAILURE

BSP Excretion	Patients (No.)	Mean BSP on Entry (%)	Mean BSP After Therapy (%)	Patient's Response to Treatment
Improvement.....	23	37.2	9.0	All satisfactory
No improvement...	7	16.1	22.1	5 patients were refractory to treatment; 1 showed moderate improvement; 1 showed good response

Serum bilirubin values were obtained in fifty-three patients; the level at the initial study was abnormal (1.0 mg. per cent or greater) in fourteen patients or 26.4 per cent of the group. A summary of the serum bilirubin determinations in relation to the venous pressure in these fourteen patients is presented in Table IV. Other authors[4,9,10] have reported a higher incidence of hyperbilirubinemia but have not rigorously excluded patients with proven or suspected pulmonary infarction as was done in our material.

The total protein, albumin and globulin of the serum were determined in fifty-six patients (Table V), values for total protein ranging from 4.5 to 8.0 gm. per cent with a mean of 6.48 for total protein, 3.3 for albumin and 3.8 for

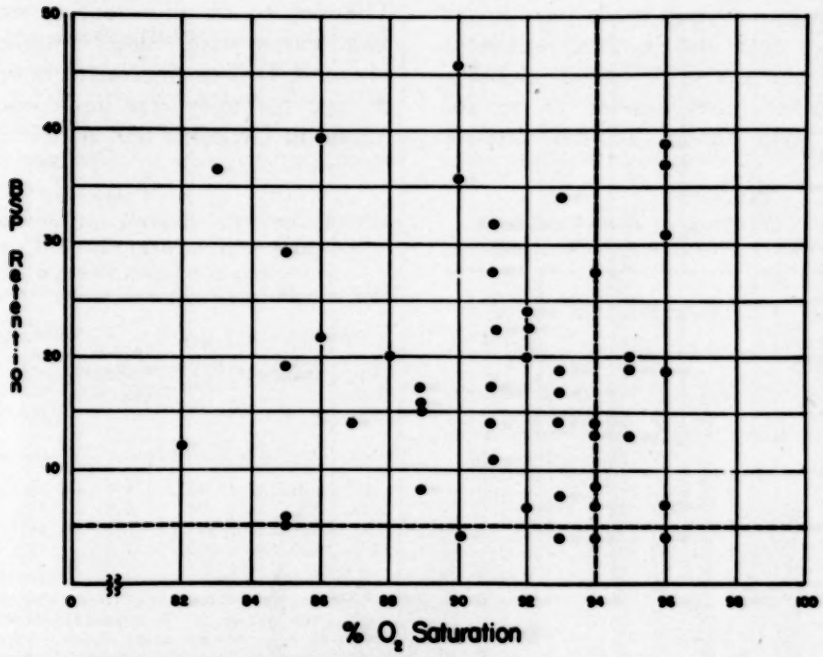


FIG. 2. The percentage of bromsulfalein retention and the arterial oxygen saturation at the initial study in forty-eight patients.

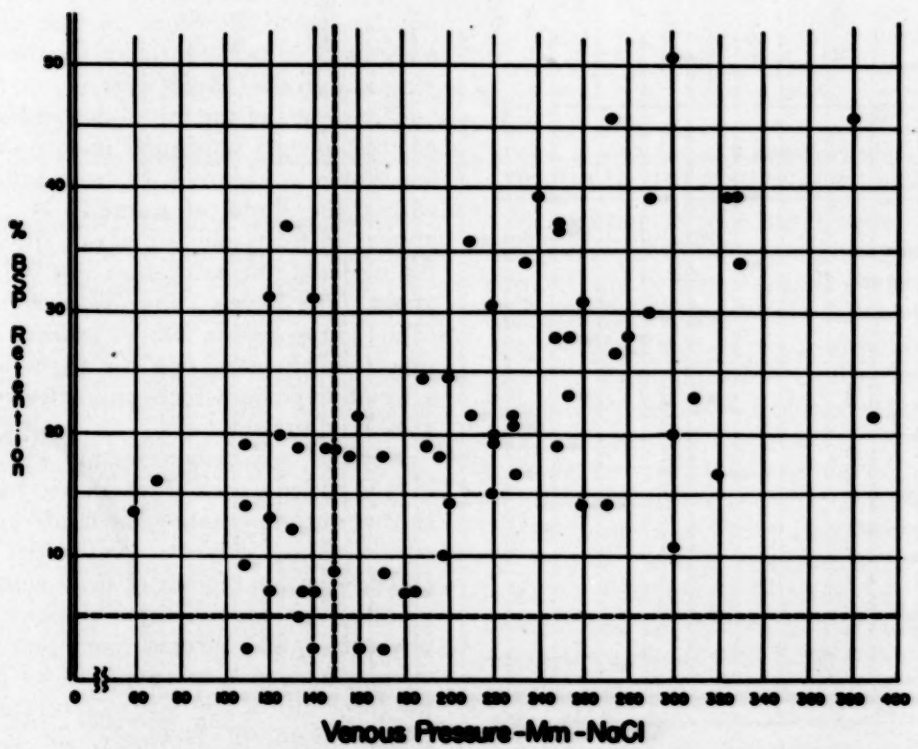


FIG. 3. The percentage of bromsulfalein retention and the venous pressure at the initial study in seventy patients.

globulin. In thirty-five of fifty-six patients (63 per cent) serum albumin levels were lower than 3.5 gm. per cent and in three instances were under 2.0 gm. per cent. Serum globulin levels, on the other hand, tended to be abnormally high with fifteen of the fifty-six patients (23 per cent) showing levels of 3.5 gm. per cent or greater. It was observed that hyperglobulinemia was more common in the individuals with rheumatic or luetic heart disease.

Abnormality of the thymol turbidity (Table II) was noted in 36.5 per cent of the entire group. The degree of abnormality was moderate in most cases, with values ranging from 4.3 to 11 units. It is of interest to note that while the thymol turbidity test gave essentially similar results in Groups I and II, the cephalin-cholesterol flocculation test, on the other hand, was positive twice as often in the city hospital patients (35 per cent) as in the University Hospital group (18 per cent).

TABLE IV

SERUM BILIRUBIN IN RELATION TO VENOUS PRESSURE IN FOURTEEN PATIENTS WITH HYPERBILIRUBINEMIA

Patient	Venous Pressure mm. NaCl Solution	Blood Bilirubin mg. %		
		Total	Direct	Indirect
C. J.	85	1.1	0.6	0.5
J. B.	130	1.1	0.6	0.5
J. S.	150	1.1	0.6	0.5
E. K.	200	1.1	0.5	0.6
M. K.	210	1.0	0.6	0.4
H. G.	230	1.1	0.3	0.8
M. J.	235	1.3	0.6	0.7
G. J.	250	2.6	0.8	1.8
L. W.	250	2.1	1.3	0.8
L. C.	270	1.3	0.8	0.5
I. L.	290	2.2	0.6	1.6
W. M.	310	1.2	0.8	0.4
W. B.	390	1.0	0.5	0.5
G. S.	...	1.3	0.8	0.5

TABLE V

SERUM, ALBUMIN AND GLOBULIN IN FIFTY-SIX PATIENTS

Range in gm. %	Albumin	Globulin
	No. of Determinations	
0 to 0.9	0	0
1.0 to 1.4	2	0
1.5 to 1.9	1	2
2.0 to 2.4	2	8
2.5 to 2.9	10	13
3.0 to 3.4	20	18
3.5 to 3.9	14	9
4.0 to 4.4	5	2
4.5 to 4.9	2	3
5.0 to 5.4	0	1
	56	56

TABLE VI

RESULTS OF THE DETERMINATION OF BROMSULFALEIN, BILIRUBIN AND HEPATIC VEIN AND FEMORAL ARTERY BLOOD OXYGEN IN FOUR PATIENTS

Patient	Diagnosis*	BSP Retention (%)	Blood Bilirubin (mg. %)	Arterial O_2 Saturation (%)	Hepatic O_2 Saturation (%)	Arterial-Hepatic Venous O_2 Difference (vols. %†)
I. L.	R.H.D.	25	1.4	94	29	8.2
L. W.	P.E.	34	0.8	93	46	8.4
L. S.	E.H.D.	12	0.7	84	50	6.0
M. J.	H.C.V.D.	30	1.4	91	44	10.4

* All patients in chronic heart failure with edema: R.H.D. = rheumatic heart disease; P. E. = pericardial effusion, ? tuberculous; E. H. D. = emphysema heart disease, "chronic cor pulmonale"; H. C. V. D. = hypertensive cardiovascular disease

† Normal value 4.5 ± 0.8 vols. %.[27]

The results of the initial determination of the arterial oxygen saturation in forty-five patients are shown in Figure 4. In twelve the value was within the limits of normal, 94 per cent or above; in thirty-one, or about three-fourths of the patients, the saturation was 90 per cent or above. The lowest value observed was 83 per cent. These results are in accord with others reported,[22,27] indicating the slight to moderate arterial hypoxia which characterizes the congestive failure state.

Hepatic vein catheterization was carried out in four patients each of whom had long-standing cardiac decompensation and moderate to marked edema. These subjects were under continuous observation for periods of from eight to twenty months. In one of these patients, with emphysema and chronic cor pulmonale, the arterial oxygen saturation was 84 per cent; in the three others the oxygen saturation was only slightly reduced. However, all four patients showed significant reduction in the oxygen saturation of the blood sample from the hepatic vein as well as clear-cut widening of the arterial-hepatic venous oxygen difference. The data are summarized in Table VI.

OBSERVATIONS

The results of the present study are generally in agreement with those previously reported.[3,5–10] Congestive failure is usually associated with alterations in the biochemical tests of liver function. This is particularly true for the excretion of bromsulfalein and to a lesser extent involves a disturbance of bilirubin metabolism. In general the flocculation and turbidity tests are less frequently altered. Other abnormalities reported in the literature, but not searched for in this series, include elevated serum alkaline phosphatase,[10,23] increased urinary urobilinogen excretion[5,9] and decreased blood prothrombin.[24]

The low serum albumin found in more than half of these patients may represent altered liver function reflecting disturbed albumin production. Also to be considered, however, is the role of reduced protein in the diet, impaired intestinal absorption of protein, or both.

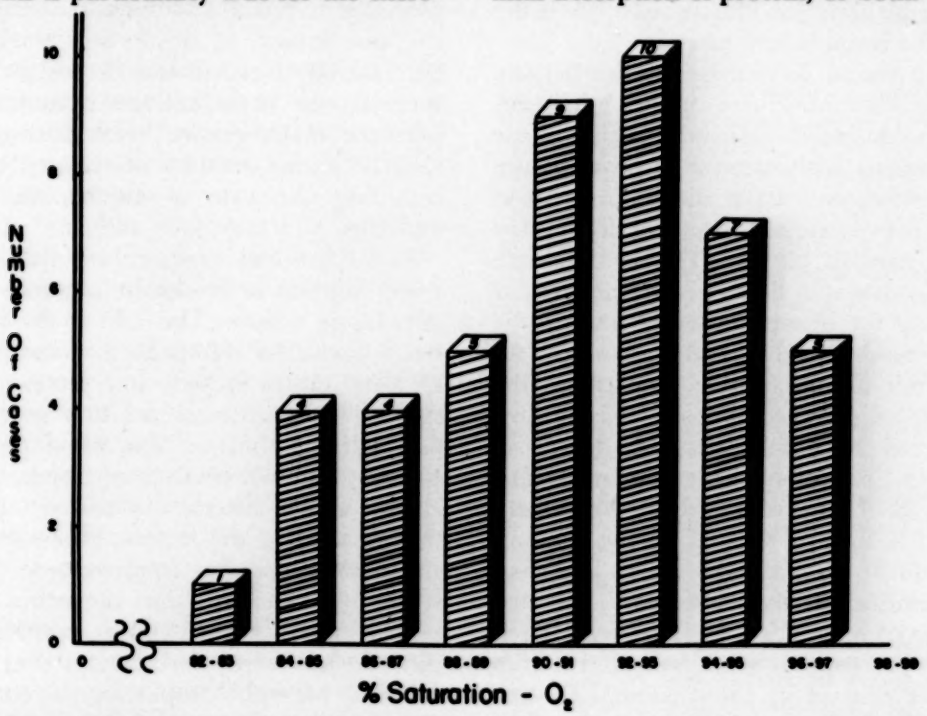


FIG. 4. The percentage of arterial O_2 saturation in forty-five patients with congestive heart failure.

It is possible that the positive cephalin flocculation and thymol turbidity tests reflect changes in the patient related to the primary disease, rather than the congestive failure as such. This is suggested by the observation that the results obtained with these tests were abnormal more often in patients with valvular heart disease than in the remainder of the group. Kissane and associates,[25] studying patients with heart disease, also found the highest incidence of positive cephalin-cholesterol flocculation tests in those with rheumatic or syphilitic heart conditions. It is of interest that hyperglobulinemia was also more frequent in this group in the present study.

The pathogenesis of the changes in liver function continues to be a source of speculation. As pointed out in Rich's classic investigation[2] the hyperbilirubinemia of heart failure is a product of diminished excretory capacity and increased bilirubin formation. His studies indicated the important relationship between anoxemia and bilirubin excretion. It was also shown by Rich that the anoxemia of anemia in humans and that induced in a gas chamber in animals produced in the liver either centrilobular atrophy or, in severe states, centrilobular necrosis, the same histopathologic features that are seen in chronic passive congestion. It is evident in our data that patients with heart failure have both anoxic and stasis anoxia, although the latter seems to predominate. Sherlock[26] has recently suggested that marked venous pressure elevation may produce mechanical obstruction of the bile canaliculi with regurgitation jaundice. Our results would indicate a trend toward higher concentrations of serum bilirubin in association with the higher levels of venous pressure, al-

though none of our subjects showed the degree of venous hypertension of Sherlock's patient. It is also evident that the impaired excretion of bromsulfalein correlates more accurately with the increase in venous pressure. However, it is possible that the correlation is artificial as the venous pressure elevation may merely reflect the severity of the heart failure process.

The more recent knowledge of the hepatic blood flow in man introduces another important factor in considering the altered function of the liver. In patients with congestive heart failure Myers and Hickam[27] have shown that blood flow to the liver is altered in proportion to the changes in cardiac output. The considerable reduction in hepatic flow which may occur would modify the interpretation of tests of the liver's excretory capacity. Although our data do not permit a quantitative estimate of the contribution of reduced hepatic blood flow to the altered liver function, the degree of bromsulfalein retention generally paralleled the severity of the heart failure in the present study and fell toward normal as the patients responded to treatment. However, in many instances significant dye retention persisted after cardiac compensation was restored. Ingelfinger[28] has reported that blood is cleared of from 10 to 15 per cent of its bromsulfalein content per minute in normal subjects; while in those with cardiac failure the figures range from 6 to 8 per cent. Blumberg and Schloss[29] have also introduced evidence that cardiac decompensation further impairs the pattern of hepatic function in patients with primary liver disease. A final appraisal of the factor of reduced hepatic blood flow must await more precise methods.

Although in this study arterial hypoxia could not be quantitatively correlated with the degree of impairment of liver function, the oxygen content of blood in the hepatic vein is probably of greater significance. As shown by our observations and those of Myers[27] hypoxia at this site is generally present and may be marked. It bears emphasis that these studies were conducted in patients in the resting and fasting state. The increased needs of exercise or metabolic load might well induce critical changes in hepatocellular oxidations and metabolism.

While reduced hepatic blood flow would seem important in distorting results obtained with excretory tests of liver function, abnormalities obtained with other tests of liver function such as serum alkaline phosphatase and urine urobilinogen would suggest actual hepatic dysfunction as well. This would be in keeping with the histologic changes shown to occur in congestive failure. The relative importance, in producing these changes, of increased venous pressure, hypoxia and impaired nutrition due to poor intake or absorption remains to be determined. Nevertheless, it seems likely that there is true hepatocellular dysfunction in the presence of congestive heart failure to which may be added a factor of reduced blood flow, retarding the rate of all hepatic functional activities.

It is pertinent to speculate upon certain of these hepatic activities in relation to cardiocirculatory failure. The role of the liver would be of particular significance in the inactivation of antidiuretic factors and steroid hormones, since these substances act in regulating water and salt metabolism. Studies of patients with primary parenchymal liver disease have indicated higher titers of urinary antidiuretic factors during the active illness, with lower titers accompanying improvement.[30] Similarly it has been shown[31] that the urine of patients with congestive heart failure contains an antidiuretic factor which is not present in control subjects. Merrill,[32] employing the concentration of sodium in sweat as an index of adrenocortical activity, found hyperfunction in six of seven patients with severe heart failure. In a similar group of subjects Parrish[33] reported increased amounts of adrenal corticoids in the urine of four of ten patients. Studies in our laboratory[34] have indicated that most patients with heart failure and edema have initial eosinopenia with the appearance of higher eosinophil levels as edema is lost. This evidence for overactivity of the adrenal steroids and antidiuretic factors might be explained either on the basis of their overproduction or their reduced inactivation by the liver. If the hepatic impairment of heart failure leads to their suboptimal inactivation, this mechanism might contribute importantly to water and sodium retention. Further studies are indicated to evaluate this concept.

SUMMARY AND CONCLUSIONS

1. The results of a study of liver function in 105 selected patients with congestive heart failure are presented. The various liver function tests were performed at the same time that the

venous pressure and arterial oxygen saturation were determined.

2. Impairment of the hepatic excretory capacity for bromsulfalein was often marked, generally paralleled the severity of the heart failure process, usually improved with restoration of cardiac compensation, but often persisted at a lesser degree.

3. Flocculation and turbidity tests were less frequently abnormal, the latter usually in association with the hyperglobulinemia found in some of the patients with rheumatic or syphilitic heart disease.

4. Serum bilirubin concentrations were increased moderately in about one-fourth of the patients, particularly in those with higher levels of venous pressure.

5. The serum albumin was less than 3.5 gm. per cent in thirty-five of fifty-six patients; the serum globulin was 3.5 gm. per cent or greater in fifteen of fifty-six patients.

6. The arterial oxygen saturation was normal in many instances and only slightly to moderately decreased in most of the patients. In the patients so studied hepatic vein hypoxia was marked.

7. The impaired excretion of bromsulfalein showed a positive correlation with the height of the venous pressure; no significant correlation was observed with the degree of arterial oxygen unsaturation.

8. The altered liver physiology is discussed from the point of the view of its possible pathogenesis and its possible relationship to sodium and water metabolism in congestive heart failure.

Acknowledgment: The authors wish to acknowledge with gratitude the technical assistance of Mrs. Eleanore Brew.

REFERENCES

1. Mallory, F. B. Chronic passive congestion of the liver. *J. M. Research*, 24: 455, 1911.
2. Rich, A. R. The pathogenesis of the forms of jaundice. *Bull. Johns Hopkins Hosp.*, 47: 338, 1930.
3. Fishberg, A. M. Jaundice in myocardial insufficiency. *J. A. M. A.*, 80: 1516, 1923.
4. Meakins, J. Distribution of jaundice in circulatory failure. *J. Clin. Investigation*, 4: 135, 1927.
5. Jolliffe, N. Liver function in congestive heart failure. *J. Clin. Investigation*, 8: 419, 1929–30.
6. Kugel, M. A. and Lichtman, S. S. Factors causing clinical jaundice in heart disease. *Arch. Int. Med.*, 52: 16, 1933.
7. Cantarow, A. Studies of hepatic function II. In portal cirrhosis and congestive heart failure. *Arch. Int. Med.*, 56: 521, 1935.
8. Bernstein, M., LeWinn, E. B. and Simkins, S. Heart disease and liver function. *J. Lab. & Clin. Med.*, 28: 1, 1942.
9. Chavez, I., Sepulveda, B. and Ortega, A. The functional value of the liver in heart disease. An experimental study. *J. A. M. A.*, 121: 1277, 1943.
10. Felder, L., Mund, A. and Parker, J. G. Liver function tests in chronic congestive heart failure. *Circulation*, 2: 286, 1950.
11. New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart, p. 69. New York, 1947. Peter F. Mallon, Inc.
12. Lyons, R. H., Kennedy, J. A. and Burwell, C. S. Measurement of venous pressure by direct method. *Am. Heart J.*, 16: 675, 1938.
13. Van Slyke, D. D. and Neill, J. M. Determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. Biol. Chem.*, 61: 523, 1924.
14. Mateer, J. G., Baltz, J. I., Marion, D. F. and MacWilliam, J. M. Liver function tests. *J. A. M. A.*, 121: 723, 1943.
15. Maclagan, N. F. Thymol turbidity, a new indicator of liver dysfunction. *Nature*, 154: 670, 1944.
16. Shank, R. E. and Hoagland, C. L. A modified method for quantitative determination of the thymol turbidity reaction of serum. *J. Biol. Chem.*, 162: 133, 1946.
17. Neefe, J. R. and Reinhold, J. G. Photosensitivity as a cause of false positive cephalin-cholesterol flocculation tests. *Science*, 100: 83, 1944.
18. Hanger, F. M. Serological differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsions. *J. Clin. Investigation*, 18: 261, 1939.
19. Malloy, H. J. and Evelyn, K. A. The determination of bilirubin with the photoelectric colorimeter. *J. Biol. Chem.*, 119: 481, 1937.
20. Cohn, C. and Wolfson, W. O. Studies in serum proteins II. Rapid clinical method for the accurate determination of albumin and globulin in serum or plasma. *J. Lab. & Clin. Med.*, 33: 367, 1948.
21. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Seibel, R. E. and Evans, J. M. Studies of congenital heart disease. I. Technique of venous catheterization as a diagnostic procedure. *J. Clin. Investigation*, 26: 547, 1947.
22. Harrop, G. A. The oxygen and carbon dioxide content of arterial and venous blood in normal individuals and in patients with anemia and heart disease. *J. Exper. Med.*, 30: 241, 1919.
23. Gutman, A. B. and Hanger, F. M., Jr. Differential diagnosis of jaundice by combined serum phosphatase determinations and cephalin flocculation test. *M. Clin. North America*, 25: 837, 1941.
24. Anderson, G. M. and Hull, E. The use of dicoumarol as an adjunct to the treatment of congestive heart failure. *South M. J.*, 41: 365, 1948.
25. Kissane, R. W., Fidler, R. S., Clark, T. E. and Conn, J. J. The cephalin-cholesterol flocculation reaction in heart disease—part I. *Am. J. Med. Sc.*, 219: 48, 1950.
26. Sherlock, S. P. V. Jaundice in heart failure. *Quart. J. Med.*, 14: 222, 1945.

27. Myers, J. D. and Hickam, J. B. An estimation of the hepatic blood flow and splanchnic oxygen consumption in heart failure. *J. Clin. Investigation*, 27: 620, 1948.
28. Ingelfinger, F. J. Hepatic function with respect to bromsulfalein removal. *Bull. New England M. Center*, 9: 25, 1947.
29. Blumberg, N. and Schloss, E. M. The effect of circulatory factors on the bromsulfalein test in liver disease. *Am. J. Med. Sc.*, 213: 470, 1947.
30. Ralli, E. P., Robson, J. S., Clarke, D. and Hoagland, C. W. Factors influencing ascites in patients with cirrhosis of the liver. *J. Clin. Investigation*, 24: 316, 1945.
31. Bercu, B. A., Rokaw, S. N. and Massie, E. Antidiuretic action of the urine of patients in cardiac failure. *Circulation*, 2: 409, 1950.
32. Merrill, A. J. The mechanisms of salt and water retention in heart failure. *Am. J. Med.*, 6: 357, 1949.
33. Parrish, A. E. The bioassay of adrenal corticoids in the urine of patients with congestive heart failure. *J. Clin. Investigation*, 28: 45, 1949.
34. Evans, J. M., Wood, O. A. and Wilmer, J. G. Unpublished observations.

Early Roentgen Diagnosis in Massive Bleeding from the Upper Gastrointestinal Tract*

I. Clinical Evaluation of Safety and Reliability of the Method in 123 Patients

NORMAN ZAMCHECK, M.D., THOMAS P. COTTER, M.D., SIMON E. HERSHORN, M.D., THOMAS C. CHALMERS, M.D., MAX RITVO, M.D. *and* FRANKLIN W. WHITE, M.D.

Boston, Massachusetts

DESPITE the value of roentgenology in the diagnosis of gastrointestinal tract lesions it has not been widely used in the past for the emergency diagnosis of the cause of massive upper gastrointestinal hemorrhage, largely because of the fear of precipitating renewed bleeding. Hampton, Schatzki and others,[1–8] however, permitted carefully restricted examination of selected patients and contradicted the prevalent conservatism. At the same time they emphasized that emergency roentgen diagnosis cannot be used indiscriminately. There is need for further clarification of its indications, contraindications and complications, as well as a critical evaluation of its diagnostic reliability. These are the objects of the present study.

Emergency roentgen examination of the gastrointestinal tract of 123 severely bleeding patients was performed. The examination was earlier and more complete in almost all cases than that recommended by other workers. The patients were divided into two groups: *Group A* consisted of the first fifty-two patients examined. These were subjected to special attention and precautions not regularly available to ward patients. They were attended by a large group of roentgenologists, surgeons, ward physicians and others. Decisions regarding management were made in consultation by the several specialists. Certain patients were carefully excluded from examination. Patients were regularly accompanied to the x-ray examining room by a member of the clinical group. One resident roentgenologist (T. P. C.) performed almost all of the examinations. After return to the ward the patient was again followed closely by various members of the team. *Group B* consisted of the last seventy-one patients examined. These patients were studied with the object of determining the accuracy and safety of the emergency roentgen method when applied without the special supervision afforded patients in *Group A*. They were managed almost entirely by the resident staff. Selection of patients was made by the ward physician. They were not regularly accompanied to the x-ray department by a clinician. Eight resident roentgenologists participated in the emergency roentgen examinations; one roentgenologist (S. E. H.) performed forty of the examinations.

Age and Sex. The ages of the 123 patients ranged from thirteen to eighty-eight, averaging fifty-four years. One hundred one of the patients were male, twenty-two female.

Severity of Bleeding. All patients manifested gross hematemesis or tarry stools or both, and were considered medical emergencies at the time of admission. Many were admitted in shock. Patients with occult bleeding were not included in the study. One indication of the degree of blood loss suffered may be gained from the

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and the Department of Roentgenology, Boston City Hospital, and the Departments of Medicine and Roentgenology, Harvard Medical School, Boston, Mass. This study was supported in part by a grant from the U. S. Public Health Service.

lowest hematocrit obtained on the patients. In Table I it may be seen that of 102 patients on whom such information was obtained, fifty or approximately one-half had a hematocrit of 27 per cent or less, and seventeen had values below 20. All patients required transfusions.

TABLE I

HEMATOCRIT LEVELS

Hematocrit Value	Lowest Hematocrit Observed No. of Patients		Hematocrit at Time of Roentgen Examination No. of Patients	
<20	17		1	
20-27	33	50 (49%)	14	15 (13%)
28-35	45		52	
>35	7	52 (51%)	47	99 (87%)
Total		102		114

Preparation for Emergency Gastrointestinal X-ray Examination. With few exceptions, the patients were prepared for examination in the routine manner. All oral intake was stopped for a period of eight to twelve hours prior to the scheduled examination. Transfusion was vigorously instituted with the aim of raising the patient's hematocrit to 28 or higher before sending him to the examining room. (Table I.) Additional blood, typed and crossmatched, was kept in readiness on the ward for prompt use if needed. The x-ray requisition form was specially marked to ensure that the patient would not be handled in a routine manner by a roentgenologist unaware of his precarious state. On the morning of the examination, prior to leaving for the x-ray examining room, the patient was rechecked by the house physician for signs of active bleeding; in some cases examination was postponed.

Contraindications to Early Roentgen Examination. In addition to the fifty-two patients of Group A examined roentgenographically twenty-three others admitted during the same period were not sent for emergency x-ray examination. They comprised the following groups:

1. Six patients readmitted with known diagnoses of duodenal ulcers confirmed previously by roentgen examination were not re-examined since the present bleeding episodes appeared clearly related to these lesions.

2. Twelve patients were so seriously ill that the procedure of roentgen examination was not considered safe. Three of these were sent promptly to the operating room for emergency laparotomy after the diagnosis of bleeding esophageal varices had been excluded. Six patients with cirrhosis of the liver died without recovering sufficiently to permit roentgen examination. Despite many transfusions, three other patients without cirrhosis died within twenty-four hours without recovering from shock sufficiently to permit either x-ray examination or surgical intervention. Duodenal ulcers were revealed at autopsy as the cause of bleeding in two patients; in the third, rupture of the gastric mucous membrane was found at the cardio-esophageal junction (Mallory-Weiss syndrome[12]).

TABLE II

HOSPITAL DAY ON WHICH INITIAL ROENTGEN EXAMINATION WAS PERFORMED

Hospital Day	No. of Patients
Day of admission	10
Day after admission	36
Two days after admission	28
Three days after admission	19
Four to seven days after admission	24
More than seven days after admission	6*
Total	123

*These 6 patients were either actively bleeding at the time or had been actively bleeding shortly before examination.

3. One hemiplegic patient was unable to cooperate sufficiently to permit the procedure. Four patients were not examined for various other reasons.

Since the decision for withholding examination of patients in group B was made by the resident staff, the number of examinations withheld during the latter period of the study and the reasons therefor are not known.

Time Interval before Roentgen Examination. With the exception of the patients described above, all patients were sent to the x-ray examining room as soon as they could be prepared properly. Fluoroscopy was usually scheduled for the morning after admission.

Ninety-three of the 123 patients were examined within three days after admission. (Table II.) Examination of patients in Group A was postponed when one or more of the following conditions persisted on the morning of the scheduled examination: (1) Evidence of active bleeding, consisting of gross hematemesis or

liquid melena; a solid black stool did not warrant delaying the examination; (2) shock of unequivocal degree, manifested by a definite fall in blood pressure, unexplained rise in pulse, undue pallor or cooling of the skin in patients whose blood volume had previously been adequately compensated by transfusion and fluid replacement; (3) temporary inability to cooperate, such as that caused by incipient delirium tremens or hepatic stupor. When delayed for such reasons the examination was rescheduled for the following morning.

Three patients were sent back to the wards from the x-ray department without examination: one patient who passed a large bloody stool on arrival at the department, another who arrived in frank shock, and a severe alcoholic patient who experienced a sudden convulsive seizure at the beginning of the roentgen examination.

*The Roentgenoscopic Examination.** At the beginning of the study an attempt was made to adjust the examination to the patient's clinical condition. Accordingly, in the early cases the roentgenologist proceeded slowly and cautiously. The clinician was alert for the earliest sign of renewed bleeding. The patient was permitted a minimum of active movement and the examiner and attendants substituted passive activity whenever possible. He was lifted on and off the examining table if necessary. The patients were carefully turned from the supine into the prone and various oblique positions. Three patients in Group A were considered too ill to stand and were examined only in the recumbent position without abdominal palpation or pressure. (Table III.) The forty-nine remaining patients were able to stand and the studies were begun with the patient erect and were continued in the supine, prone and oblique positions. Manual pressure was applied to the abdomen of forty-four of the forty-nine patients. Palpation was carried out gently with the gloved hand; excessive pressure or the sudden application of marked force was avoided. In addition to the above procedures the pressure cone was applied to the remaining five patients in order to define further questionable areas. In almost every instance the examination included the duodenal bulb and loop, and the upper jejunum as well as the esophagus and stomach. During the fluoroscopic examination many spot films were made. Following fluoroscopy routine roentgenograms were taken. After the examination the patient was returned promptly to the ward. Six-hour and twenty-four-hour post-examination films were not taken routinely.

TABLE III

EXTENT OF INITIAL ROENTGEN EXAMINATION

Extent	Group A No. of Patients	Group B No. of Patients	Total No. of Patients
Complete examination performed	5	38	43
Pressure cone* studies omitted only	44	3	47
Examination in standing position omitted only	0	3	3
Both pressure cone* studies and standing omitted	3†	7	10
Examination unsatisfactory for other reasons	0	4	4
Extent of examination unknown‡	0	16	16
Total	52	71	123

*Gentle manual pressure was applied in almost every instance.
†Manual pressure and abdominal palpation also omitted.
‡It may be assumed that most of these were essentially complete examinations.

During the initial study the relative safety of the procedure became apparent, and in thirty-eight patients of Group B a complete roentgenoscopic examination was performed which included routine use of the pressure cone. (Table III.) In thirteen instances the examination was complete with the exception of the application of pressure and/or the use of the erect position. In sixteen patients no record was made of the completeness of the examination although it may be assumed that most of these were complete examinations. The examination of four patients in Group B was unsatisfactory for various reasons.

Follow-up Examinations. (Tables IV and V.) In order to evaluate the accuracy of the emergency roentgen examinations, it was planned that at least one follow-up examination be performed on all patients. Subsequent examinations were omitted in sixteen instances in Group A and in eleven instances in Group B. Five diagnostic methods were utilized for follow-up studies on ninety-six patients (thirty-six in Group A, sixty in Group B). These consisted of roentgen examination, gastroscopy, esophagos-

* Details concerning the nature of the barium mixtures utilized and other technical aspects of the roentgenographic procedure will be published in a subsequent paper.[9]

copy and gross and microscopic examination of lesions seen at operation or at postmortem examination. About one-half of the patients who had follow-up examinations were examined by more than one method. Twenty-nine of the patients eventually came to surgery.

TABLE IV

PATIENTS EXAMINED BY EACH FOLLOW-UP PROCEDURE

	No. of Patients
Roentgen examination	62
Gastroscopy	47
Surgery	29
Esophagoscopy	9
Autopsy	6

TABLE V

FOLLOW-UP EXAMINATIONS

		No. of Patients
1. Single method used for follow-up examination		49
x-ray	24 (28 exams)	
gastroscopy	14	
esophagoscopy	1	
surgery	9	
autopsy	1	
2. More than one method used		47
x-ray + gastroscopy	21	
x-ray + surgery	7	
x-ray + gastroscopy + surgery	5	
x-ray + esophagoscopy	3	
esophagoscopy + autopsy	2	
x-ray + esophagoscopy + surgery + autopsy	1	
surgery + gastroscopy	5	
surgery + esophagoscopy	1	
gastroscopy + surgery + autopsy	1	
x-ray + esophagoscopy + gastroscopy	1	
3. No follow-up examination		27
	Total	123

Final Diagnoses. The final diagnoses achieved after completion of all examinations on the 123 patients are listed in Tables VI and VII. A total of 189 findings were made on 116 patients. (Table VI.) A single lesion was diagnosed in sixty-three patients (Table VI) and multiple lesions in fifty-three patients. (Table VII.) The most common lesions consisted of duodenal ulcer (diagnosed sixty-nine times), gastritis

TABLE VI

SUMMARY OF FINAL DIAGNOSES IN 116 PATIENTS*

Diagnostic Finding	No. of Patients in Whom the Diagnostic Finding Occurred: As a Single Final Diagnosis	As Part of a Multiple Final Diagnosis	Total No. of Times Finding Diagnosed
Gastric ulcer	12	14	26
Duodenal ulcer	31	34†	65†
Gastritis	5	35	40
Esophageal varices	2	3	5
Gastric cancer (ulcer)	3	0	3
Stomal ulcer	0	2	2
Duodenitis	1	2	3‡
Hiatus hernia	2	18	20
Duodenal diverticulum	3§	10	13§
Gastric diverticulum	0	2	2
Undefined esophageal lesion	1	0	1
Cancer head of pancreas with duodenal erosion	1	0	1
Uremia	1	0	1
Multiple myeloma	1	0	1
Choriocarcinoma of jejunum	0	1	1

*No diagnostic findings noted in 7 patients.
†One patient had 5 duodenal ulcers (4 healed and 1 active).
‡Two other patients diagnosed initially as duodenitis developed well defined ulcer craters subsequently.
§Two in one patient.

(forty times) and gastric ulcer (twenty-six times). Esophageal varices were proven in five patients, gastric cancer in three patients. Two patients had marginal ulcers and three patients had findings consistent with duodenitis. Hiatus hernias and duodenal diverticula, usually considered incidental findings, were noted twenty and thirteen times, respectively. The sole finding of hiatus hernia in one patient, minimal gastritis in a second, duodenal diverticulum in two others, and both hiatus hernia and duodenal diverticulum in two others, and both hiatus hernia and duodenal diverticulum in a fifth were considered as questionable or unlikely causes for bleeding. No further studies were available in four of these patients. No final diagnosis was established in seven other patients.

Six of these were incompletely studied, some refusing further studies, others leaving the hospital against advice. No cause for bleeding was found in the seventh patient despite extensive study at this hospital as well as at numerous other hospitals for repeated episodes of gastrointestinal bleeding extending over several years.

TABLE VII

PATIENTS WITH MULTIPLE FINAL DIAGNOSES

Diagnoses		No. of Patients
Gastric ulcer + duodenal ulcer		7
G.U.* + D.U.†	2	
G.U. + D.U. + gastritis	1	
G.U. + D.U. + gastritis + H.H.‡	1	
G.U. + D.U. + gastritis + D.Div.§	1	
G.U. + D.U. + H.H.	2	
Gastric ulcer + gastritis		6
Gastric ulcer + hiatus hernia		1
Duodenal ulcer + gastritis		14
Duodenal ulcer + gastritis + hiatus hernia		3
Duodenal ulcer + hiatus hernia		2
Duodenal ulcer + duodenal diverticulum + gastric diverticulum		1
Duodenal ulcer + duodenal diverticulum		3
Duodenal ulcer + gastric diverticulum		1
Duodenal ulcers (1 active crater, 4 healed) + metastatic choriocarcinoma to jejunum (2 nodules)		1
Marginal ulcer, duodenal ulcer deformity + duodenal diverticulum		1
Marginal ulcer + hiatus hernia		1
Esophageal varices + duodenal ulcer + hiatus hernia + duodenal diverticulum		1
Esophageal varices + gastritis		1
Esophageal varices + hiatus hernia		1
Gastritis + hiatus hernia		4
Gastritis + duodenal diverticulum		1
Gastritis + hiatus hernia + duodenal diverticulum		1
Gastritis + duodenitis		1
Gastritis + hiatus hernia + duodenitis		1
Hiatus hernia + duodenal diverticulum		1
	Total	53

*Gastric ulcer; †duodenal ulcer; ‡hiatus hernia; §duodenal diverticulum.

Reliability of Initial Roentgen Examination. (Table VIII.) The initial roentgen diagnoses of ninety-two patients were correct. Since the initial roentgen findings of twenty of these were unequivocal and consistent with the clinical findings, repeat studies were not performed. The diagnoses of the remaining seventy-two cases were confirmed by one or more means.

Diagnostic errors were made at the initial roentgen examination of seven patients. (Table IX.) Two ulcers, one gastric and one duodenal, were not visualized. Another unsuspected gastric ulcer was discovered at laparotomy undertaken for a duodenal ulcer, erroneously diagnosed. Two patients diagnosed originally as "antral gastritis" proved on subsequent examination to have prepyloric ulcers. One incorrect diagnosis of esophageal varices was made at initial ex-

TABLE VIII

RELIABILITY OF INITIAL ROENTGEN EXAMINATION

	Group A	Group B	Total
	No. of Patients	No. of Patients	No. of Patients
1. Initial roentgen diagnosis correct	41	51	92
2. Initial roentgen diagnosis correct; additional findings noted subsequently	0	6	6
3. Initial roentgen diagnosis incorrect*	6	8	14*
4. No satisfactory roentgen diagnosis made	5	6	11
	52	71	123

*Includes 7 patients subsequently shown to have gastritis and 5 others correctly diagnosed on repeat roentgen examination.

TABLE IX

INACCURATE EMERGENCY ROENTGEN DIAGNOSES

	Group	Inaccuracy	Means by Which Diagnosis Finally Made	Initial Roentgen Examination
1.	B	Gastric ulcer missed	Gastroscopy and x-ray	Unsatisfactory; patient unable to cooperate or stand at emergency examination
2.	B	Duodenal ulcer missed	X-ray	Unsatisfactory; same
3.	A	Duodenal ulcer erroneously diagnosed; gastric ulcer missed	Surgery	Incomplete; patient actively bleeding; in desperate condition
4.	A	Incorrect diagnosis of esophageal varices made initially	X-ray and esophagoscopy	Incomplete; 84 year old man; poor cooperation
5.	B	Esophageal varices missed; hiatus hernia diagnosed correctly	Esophagoscopy and autopsy	Unsatisfactory, despite complete examination; patient in marginal shock
6.	B	Prepyloric ulcer missed; original diagnosis "antral gastritis"	X-ray	Complete
7.	B	Prepyloric ulcer missed; original diagnosis "antral gastritis"	X-ray	Complete

amination, and in another patient varices were missed.

Seven patients proved to have gastritis at subsequent gastroscopic examination (six patients) and at operation (one patient) not diagnosed at initial roentgen examination. (Table x.) Subsequent examination of six other patients not only confirmed the presence of the initial roentgen diagnosis (duodenal ulcer four cases, and gastritis two cases) but also revealed additional findings (Table xi), including duodenal ulcers in three patients, esophageal varices, hemorrhagic atrophic gastritis and a small gastric ulcer, respectively, in the other three.

TABLE X
CASES OF GASTRITIS DIAGNOSED SUBSEQUENT TO INITIAL ROENTGEN EXAMINATION

	Group	Diagnoses	Means by Which Diagnosis Was Made	Extent of Initial X-ray Examination
1.	A	Atrophic gastritis	Gastroscopy	Incomplete; no pressure or standing
2.	A	Atrophic gastritis	Gastroscopy	Incomplete; no pressure or standing
3.	A	Superficial hemorrhagic gastritis	Gastroscopy	Incomplete; no pressure or standing
4.	A	Hemorrhagic gastritis with large superficial ulceration of gastric mucous membrane just below esophagus (adjacent to hiatus hernia seen at x-ray)	Gastroscopy	Incomplete
5.	B	Hemorrhagic gastritis; hiatus hernia diagnosed correctly at initial roentgen examination	Gastroscopy	? Patient bleeding when sent to x-ray
6.	B	Antral gastritis; hiatus hernia diagnosed correctly	Gastroscopy and x-ray	Complete
7.	B	Chronic hemorrhagic gastritis; hiatus hernia and duodenal diverticulum diagnosed correctly	Surgery and autopsy; gastroscopy not done	Incomplete

The initial roentgen diagnosis was confirmed in twenty-seven of the twenty-nine patients who were operated upon, either as emergency or as elective procedures. (Patient No. 3 Table ix, and patient No. 7 Table x.)

In one case of advanced carcinoma of the fundus of the stomach the roentgenologist initially was not able to exclude the possibility of clotted blood simulating neoplasm. When the defect remained constant at subsequent roentgen examination, however, the diagnosis was confirmed and finally proven at operation.

Rapid Healing of Peptic Ulcers. Five well defined gastric ulcers healed rapidly. Three of these, clearly visualized on the day after admission to the hospital, and confirmed gastroscopically, were roentgenologically invisible seven, ten and fourteen days after admission. A fourth ulcer, 2 cm. in width and 1 cm. deep, diminished in size rapidly and was entirely healed at operation approximately thirty days after the initial x-ray. The fifth was completely healed at operation three weeks after the initial examination. Two duodenal ulcers showed complete disappearance on repeat roentgen study performed seven and nine days after the initial examinations.

Relation between Completeness of Examination and Reliability of Diagnosis. Only two of the seven cases (Table ix) erroneously diagnosed at initial roentgen examination were examined completely. Both of these cases, called initially "antral gastritis," proved on later roentgen examination to have prepyloric ulcers. Subsequent complete roentgen examination revealed the correct lesions in three other patients. Only one of the seven gastritis cases overlooked at initial roentgen examination were examined completely at that time. (Table x.) It is of interest that all three cases misdiagnosed despite complete examinations had lesions of the gastric antrum.

Seventeen examinations in Group B were considered unsatisfactory for one or more reasons. (Table xii.) Incomplete examinations were performed on thirteen patients, i.e., pressure studies and/or examination in the standing position were omitted. (Table iii.) Four of these patients were not able to cooperate sufficiently. The presence of "retained secretions" in the stomach prevented adequate examination of two other patients. The stomach of one patient emptied so rapidly that an overlying loop of bowel prevented adequate examination of the duodenal cap. One other examination was considered unsatisfactory for another unknown reason. Six errors were made in this group of seventeen patients. No satisfactory diagnosis was made in three other patients of this group. Eight patients were correctly diagnosed despite the incomplete examination. In the thirty-eight patients of group B who were examined completely and satisfactorily, seven errors were made and no satisfactory diagnosis was made in two instances. From these data it would appear that the chances of making an error in

diagnosis or of achieving no satisfactory diagnosis were approximately twice as great in the incompletely or unsatisfactorily examined group as in the group of complete and satisfactory examinations.

Bleeding Following Initial Roentgen Examination. (Tables XIII and XIV.) One hundred one of the 123 patients failed to show any evidence of continued or renewed bleeding at any time following the initial roentgen examination: none experienced hematemesis; the stool tests for blood showed prompt and uniform fall in intensity; there was no change in the hematocrit or in the pulse or blood pressure to suggest renewed bleeding.

Ten patients showed questionable, insignificant or non-serious bleeding after the initial examination. In every instance the bleeding either bore no direct relationship to the roentgen examination or was too mild to be of importance even if precipitated by the examination.

Twelve patients showed evidence of severe bleeding after roentgen examination, three in group A and nine in group B. Eight of these were actively bleeding at the time of the examination. One patient (No. 9) was bleeding so severely that immediate surgery was imperative, and at the request of the surgical

TABLE XI

ADDITIONAL FINDINGS NOTED ON SUBSEQUENT EXAMINATIONS OF PATIENTS WITH A CORRECT INITIAL ROENTGEN DIAGNOSIS

	Group	Initial X-ray Diagnosis Correctly Made	Additional Finding	Method of Subsequent Examination	Extent of Initial X-ray Examination
1.	B	Superficial duodenal ulcer	Hemorrhagic atrophic gastritis	Gastroscopy	Complete
2.	B	Duodenal ulcer	Small gastric ulcer; not visible on repeat complete x-ray examination	Gastroscopy	Incomplete
3.	B	Gastritis	Duodenal ulcer	Subsequent x-ray	Unsatisfactory; stomach emptied rapidly and overlying jejunal loop obscured cap
4.	B	Duodenal ulcer	Four additional healed duodenal ulcers and metastatic carcinoma of jejunum	Autopsy	Complete
5.	B	Duodenal ulcer and hiatus hernia	Esophageal varices	Esophagoscopy and x-ray	Complete
6.	B	Gastritis, duodenitis and hiatus hernia	Duodenal ulcer crater	X-ray	Complete

TABLE XII

RELATION BETWEEN COMPLETENESS OF INITIAL EXAMINATION AND RELIABILITY OF FINDINGS (GROUP B PATIENTS ONLY)

Examination	No. of Patients*	Initial Exam. Wholly or Partly Unreliable† (No. of pts.)	No Satisfactory Diagnosis Made (No. of pts.)	Total
Satisfactory (includes complete examinations only)	38	7	2	9
Unsatisfactory (includes incomplete examinations)	17	6	3	9

*Sixteen patients are omitted because record of the extent of examination was not made.

†Includes partly correct examinations.

TABLE XIII

GASTROINTESTINAL BLEEDING AFTER EMERGENCY ROENTGEN EXAMINATION

Severity of Bleeding after Examination	Group A No. of Patients	Group B No. of Patients	Total No. of Patients
1. None	47	54	101
2. Non-serious or questionable bleeding	2	8	10
3. Severe	3	9	12
Total	52	71	123

consultant he was sent to the examining room within a few hours after admission and examined completely, despite his precarious condition, in order to identify the site of bleeding. Seven patients (Nos. 1, 2, 3, 6, 8, 11 and 12) had been bleeding continuously and actively right up to the time of the examination, performed on the second, third (three patients), fourth (two patients) and sixth hospital days, and the post-examination bleeding could not be attributed unequivocally to the examination. Four of these patients died subsequently. One patient (No. 12) died in hepatic coma several days after examination; another (No. 11) died several weeks later of intracranial hemorrhage from metastatic choriocarcinoma. The third patient (No. 8) died following emergency surgery performed for intractable hemorrhage. Patient No. 3 died ten days after operation as a result of postoperative complications.

TABLE XIV

PATIENTS MANIFESTING SEVERE HEMORRHAGE FOLLOWING EARLY ROENTGEN EXAMINATION

Case No., Sex & Age	Group	Evidence of Bleeding	Initial Roentgen Examination: Time	Initial Roentgen Examination: Extent	Diagnosis	Outcome
1., M, (49)*	A	Patient bled intermittently on each of 3 days prior to examination; vomited bright red blood after return to ward	4th hospital day	Incomplete, examined in recumbency only, without pressure	Diffuse hemorrhagic gastritis	Emergency surgery; recovered
2., M, (44)	A	Bled constantly day of admission, day of examination and following day	Day after admission	Incomplete, examined in recumbency only, without pressure	Antral gastritis and duodenitis	Emergency surgery; recovered
3., M, (49)	A	Patient bled continuously for 3 days prior to examination, and for 2 days after examination	3rd hospital day	Incomplete, examined in recumbency only, without pressure	Gastric ulcer	Emergency surgery; died 10 days after operation
4., M, (35)	B	Many liquid bloody stools and hematemeses, fall in B.P. and rise in pulse for 24 hr. after examination	24 hr. after admission	Complete	Marked gastritis and small duodenal ulcer and duodenitis	Bleeding subsided spontaneously
5., F, (49)	B	Hematemesis, 700 cc. 6 hr. after examination; rise in pulse without fall in B.P.	Day after admission	Complete	Antral gastritis and hiatus hernia	Bleeding subsided spontaneously
6., M, (52)	B	Patient was actively bleeding for 2 days prior to x-ray; continued to bleed after examination; loose black stool with dark blood 6 hr. after examination	2 days after admission	?	Hemorrhagic gastritis and hiatus hernia	Bleeding subsided spontaneously
7., M, (37)	B	Black stool associated with falling hematocrit the night after examination; continued to bleed the following day	Day after admission	Incomplete, without mechanical pressure	Gastritis (?duodenal ulcer – not seen or felt at operation)	Surgery
8., F, (75)	B	Seventy-five year old woman bleeding severely when sent to x-ray department; had bled for 4 days in hospital; clinically diagnosed as cancer of stomach; taken to operating room from x-ray	Morning of 4th day	?	Eroded artery in duodenal ulcer	Died day after operation
9., M, (71)	B	Sent to x-ray day of admission and examined despite arrival in shock; syncope and rise in pulse at x-ray; bloody stool after return to ward	Few hours after admission	Complete	Duodenal ulcer	Surgery; recovered
10., F, (51)	B	Red-black liquid stools and drop in hematocrit following examination	Day after admission	Complete	Duodenal ulcer	Bleeding subsided spontaneously
11., F, (44)	B	Patient passed black stools throughout hospital stay including after examination	6 days after admission	Complete	5 duodenal ulcers and metastatic choriocarcinoma to jejunum; (autopsy)	Bleeding subsided; died 2 wk. after examination of intracranial hemorrhage from metastases
12., M, (48)	B	Many episodes of hematemesis and black melena before and after x-ray exam. until death; examined in marginal shock; pulse elevated; B.P. depressed	3rd hospital day	Complete	Esophageal varices; (autopsy)	In hepatic coma several days later; died

*Figures in parentheses represent age.

Five other patients (Nos. 2, 4, 5, 7 and 10) who showed unquestionable evidence of bleeding following the initial roentgen examination were examined within twenty-four hours after admission, and the responsibility of the roentgen examination for the continued bleeding could not be clearly evaluated.

The principal diagnoses noted in the twelve patients with severe bleeding following roentgen examination consisted of duodenal ulcer (three patients), gastritis (six patients), esophageal varices (one patient) and gastric ulcer (one patient). One patient had multiple duodenal ulcers and metastatic choriocarcinoma of the jejunum. Complete roentgen examination was performed on six of the twelve patients, incomplete examination on four. The extent of the examination was not described in two patients.

COMMENTS

Importance of Early and Correct Diagnosis. It is generally agreed that the mortality in patients requiring emergency operations for massive hemorrhage rises with increased delay in the institution of surgical measures. Prompt, accurate diagnosis of the cause of bleeding in such patients is imperative. Lesions such as esophageal varices, which are not remediable by emergency surgery, must be excluded. Although massive bleeding from hemorrhagic gastritis may continue for several days, it usually subsides with medical management. Accordingly, most surgeons hesitate to advise operation as freely as they do when the hemorrhage is caused by a peptic ulcer. Furthermore, the surgical approach to the site of bleeding sometimes varies with the location of the lesion. The thoracoabdominal or transthoracic approach may be preferable, or even essential, for certain lesions. Identification of the site of bleeding at operation is sometimes difficult and valuable time may be lost in time-consuming exploratory procedures. Occasionally, no site of bleeding may be found. When the diagnosis is known prior to operation, the duration of operation is shortened. The use of minimal amounts of anesthetic agents is particularly desirable for patients with liver disease who are known to tolerate major operations poorly.[18]

Special Dependence of the Physician on Laboratory Aids to Diagnosis. At a large city hospital the making of an early and[21,22] accurate diagnosis presents certain difficulties. Massive hemorrhage is sometimes the first major symptom of gastrointestinal disease, and some patients arrive at the hospital only after prolonged hemorrhage; some are too ill to describe their illness reliably; others are poor observers of their symptoms. About one-half of the patients admitted to the Boston City Hospital because of massive gastrointestinal hemorrhage are chronic alcoholics, a fact which tends not only to reduce the reliability of the clinical history but also adds to the differential diagnosis those diseases etiologically related to alcoholism, such as esophageal varices and gastritis.

Previous experience has emphasized that the separation of patients with ruptured esophageal varices from those bleeding from other causes is highly unreliable when diagnosis is based on clinical grounds alone. Patients with varices may have no clinical signs of cirrhosis and patients with cirrhosis may bleed from ulcers. Accordingly, the bromsulphalein liver function test has been used routinely to screen patients with serious liver disease from those without severe liver disease promptly after admission.[10] Patients with markedly elevated dye retention during bleeding, consistent with the diagnosis of cirrhosis, were then further examined for esophageal varices. Emergency bedside esophagoscopy was utilized for this purpose in patients who were too ill to be moved to the x-ray examining room.[11] There remained, however, the much larger group of patients bleeding from lesions other than those of the esophagus. Roentgen examination provided the only available means for reliable prompt diagnosis.

Use of Roentgen Examination in Massive Gastrointestinal Hemorrhage. It was customary in the past to defer attempts to determine the cause of the hemorrhage by the roentgen method until the bleeding had subsided or ceased entirely and the patient's condition had improved. Any diagnostic procedure or manipulation which might increase the bleeding was carefully avoided. Roentgen studies, therefore, were of very limited usefulness. With the lowered mortality attendant on gastric surgery today the importance of early diagnosis is greatly enhanced, and recently a trend toward the earlier use of roentgen examination has occurred.[1–8] The present studies were designed to provide further information concerning the reliability of the emergency roentgen examination and its safety.

Reliability of Diagnosis. The initial examination proved to be accurate in most of the pa-

tients. Some of the erroneous findings were unquestionably the result of incomplete or unsatisfactory examinations. All participating roentgenologists noted an increased proficiency in handling this type of patient with added experience, and the somewhat better results of the first study (Group A) may possibly be attributed to the fact that a single radiologist performed all the examinations. With a cooperative patient, adequately prepared and satisfactorily examined, accuracy was greatest. Surprisingly, the presence of clotted blood in the stomach was rarely encountered and hence it was not an obstacle to successful diagnosis. Lesions which proved particularly troublesome included esophageal varices, gastritis (commonly revealed at subsequent gastroscopy) and lesions of the gastric antrum, antral "spasm," "gastritis" or "narrowing." It has been pointed out by several authors that these diagnoses may be difficult to establish clearly even in the nonbleeding patient. The use of early repeat roentgen examination was often essential for proper evaluation of the initial findings. Thus repeat examination revealed esophageal varices overlooked initially, and antral ulcers which were masked initially became apparent at later study. Although the roentgen diagnosis of gastritis was overlooked in some instances, it was made successfully in a surprisingly large number of cases. These cases were confirmed gastroscopically in almost every instance and in three instances pathologically as well. The x-ray findings of gastritis tended to disappear within a relatively few days, and it is likely that the early examination was responsible both for the accuracy in achieving the diagnosis as well as for the relatively large number of such cases diagnosed.

Multiple Diagnoses. Multiple lesions were described in many patients of the present study. In most cases it was not possible to ascertain, which of the findings was responsible for the bleeding of a given patient. Several factors may account for the frequency of multiple diagnoses: (1) Early roentgen examination and early repeat examination, when indicated, reveal lesions which may rapidly heal and not be apparent at later examination. Thus seven peptic ulcers in this series might easily have been overlooked if the roentgen examination had been delayed until two or three weeks after admission. (2) The use of the complete examination, even after one apparent finding is revealed, may uncover additional lesions. (3) The use of other diagnostic technics such as esophagoscopy and gastroscopy, in addition to the roentgen examination, facilitates diagnosis of lesions difficult to visualize roentgenographically. (4) The high percentage of alcoholics found in this hospital may account for the frequent diagnosis of gastritis. The roentgen diagnosis of this lesion, considered unreliable by some workers, has been made at this clinic with a fair degree of reliability. Gastroscopy, however, is essential for confirmation of this diagnosis in most instances. Although bleeding from duodenal diverticulum has been reported,[17] it was not proven to be the cause in any case of the present study. One patient bled clearly from a superficial ulceration in a hiatus hernia. Hiatal hernia bleeding seemed likely in a few others. In most cases, however, the hernia was an incidental finding.

Safety of the Emergency Roentgen Examination. In no case was the emergency roentgen examination clearly responsible for subsequent severe bleeding. On the other hand, the possibility that early examination exaggerated bleeding or precipitated renewed bleeding could not be excluded. More patients in Group B than in Group A were examined while bleeding actively, and more complete examinations were performed in Group B than in Group A. These facts may account for the higher incidence of post-examination bleeding in Group B. No fatalities could be ascribed to the procedure.

Greater safety could have been ensured by postponing examination until all evidence of bleeding had subsided, as was done commonly in the first group. Strict adherence to this rule, however, would have excluded from examination those patients who required accurate diagnosis most urgently, i.e., those who continued to hemorrhage and who were most likely to need emergency surgery. Management of a patient with serious hemorrhage without benefit of exact diagnosis entails a definite risk. In a large city hospital this additional risk may often exceed the risk of performing the roentgen examination. Each patient must be evaluated individually.

The data obtained in the foregoing studies of 123 patients clearly indicate that emergency examination of most patients with massive gastrointestinal bleeding is not a hazardous procedure when performed under the conditions described. At the Boston City Hospital when used along with all other methods of diagnosis

and management it has proved of unquestionable value. It should be used, however, with a clear understanding of its limitations and potential dangers.

SUMMARY AND CONCLUSIONS

The availability of emergency surgery for the management of massive gastrointestinal hemorrhage necessitates prompt and accurate diagnosis of the cause of bleeding. Since diagnosis based on clinical grounds alone is often unreliable, particularly among patients in a large city hospital, greater reliance must be placed on laboratory aids to diagnosis. In order to evaluate the safety and the accuracy of early roentgen examination, 123 patients with massive hemorrhage were studied by this method.

The initial roentgen examinations were performed by resident roentgenologists, usually as soon after admission as the patients could be prepared. Seventy-four were examined within two days after admission. The remainder were examined within seven days after admission with the exception of six patients whose active bleeding occurred on later days.

Complete roentgen examinations, including application of the pressure cone, were performed in forty-three patients. Pressure cone studies were omitted in forty-seven patients otherwise completely examined. Thirteen patients were examined only in recumbency. The extent of examination was unknown in sixteen patients.

The results of the emergency roentgen examination were compared with subsequent roentgen, gastroscopic and esophagoscopic examinations. Pathologic examination of tissue was afforded by twenty-nine operations and six autopsies.

The final diagnoses achieved included peptic ulcer diagnosed ninety-one times, (sixty-five duodenal and twenty-six gastric), esophageal varices (five times), gastric cancer (three times), gastritis (forty times); marginal ulcer (twice) and others. Multiple findings were noted on fifty-three patients. No satisfactory final diagnosis was made in twelve patients, ten of whom were considered inadequately studied.

The initial roentgen diagnosis was confirmed in ninety-two cases. Fourteen erroneous diagnoses included the following: one gastric and one duodenal ulcer overlooked; three gastric ulcers, initially diagnosed as antral gastritis (two cases) and duodenal ulcer (one case); one unsubstantiated diagnosis of esophageal varices was made, and another case was overlooked at the initial examination. The diagnosis of gastritis, not made at initial roentgen examinations of seven patients, was made at subsequent gastroscopy (six cases) and surgery (one case). Only three of the fourteen cases had complete initial roentgen examinations.

Although twelve patients bled severely at some time after returning from the roentgen examination, in no instance was it possible to establish or to disprove a causal relation between the roentgen procedure and the subsequent bleeding. Clearly, however, no deaths could be attributed to the examination.

It is concluded that emergency roentgen examination of the gastrointestinal tract may be performed with reliability, and that more extensive examinations may be performed with greater safety than was formerly believed possible. The use of early repeat roentgen examination is recommended as a valuable and safe adjunct to the initial roentgen examination.

Acknowledgment: The results of the present study emphasize the advantages of the recent trend[18–20] toward the combined management of patients with massive hemorrhage. At the Boston City Hospital patients with massive hemorrhage are admitted to the medical service and the services of various specialists are consulted promptly and decisions regarding management are made jointly. The present study would not have been possible without the collaboration of the many house physicians, surgeons, esophagoscopists, gastroscopists and pathologists. We wish to express our gratitude particularly to Drs. Max Carter, Charles S. Davidson, Isaac R. Jankelson, Steven Maddock, Charles W. McClure and Melvin P. Osborne for their professional cooperation, and to Mrs. Audrey Durkee Whitten for her assistance in compiling the data.

REFERENCES

1. Hampton, A. O. Safe method for roentgen demonstration of bleeding duodenal ulcers. *Am. J. Roentgenol.*, 38: 565–570, 1937.
2. Schatzki, R. Roentgenologic examination in patients with bleeding from the gastrointestinal tract. *New England J. Med.*, 235: 783, 1946.
3. Bohrer, J. V. Massive gastric hemorrhage with special reference to peptic ulcer. *Ann. Surg.*, 114: 510, 1941.
4. Kiefer, E. D. Jejunal ulcers and recurrent hemorrhages. *J. A. M. A.*, 120: 819, 1942.
5. Thorstad, M. J. The problem of bleeding peptic ulcer. *Surgery*, 12: 964, 1942.

6. Eads, J. T. Massive gastro-intestinal hemorrhage. *J. A. M. A.*, 131: 891, 1946.
7. Kirklin, B. R. Bleeding lesions of the gastro-intestinal tract and the roentgenologic diagnosis. *Roentgenology*, 45: 171, 1941.
8. Elmer, R. A. and Rousuck, A. A. Early roentgenologic examination in patients with upper gastro-intestinal hemorrhage. Report of 58 cases. *Gastroenterology*, 16: 552, 1950.
9. Ritvo, M., Cotter, T. P. and Zamcheck, N. Early roentgen diagnosis in massive gastro-intestinal hemorrhage. II. Roentgen aspects. *Am. J. Roentgenol.*, 66: 728, 1951.
10. Zamcheck, N., Chalmers, T. C., White, F. W. and Davidson, C. S. The bromsulfalein test in the early diagnosis of liver disease in massive gastro-intestinal hemorrhage. *Gastroenterology*, 14: 343, 1950.
11. Carter, M. and Zamcheck, N. Esophagoscopy in upper gastro-intestinal bleeding. *New England J. Med.*, 242: 280, 1950.
12. Weiss, S. and Mallory, G. K. Lesions of the cardiac orifice of the stomach produced by vomiting. *J. A. M. A.*, 98: 1375, 1932.
13. Boyce, F. F. The Role of the Liver in Surgery. Springfield, Ill., 1941. Charles C Thomas Co.
14. Berridge, F. R. Radiological aspects of gastritis. *Brit. J. Radiol.*, 15: 1, 1942.
15. Templeton, F. E. X-ray Examination of the Stomach. Chicago, 1944. Univ. of Chicago Press.
16. Schindler, R. Gastritis. New York, 1947. Grune & Stratton.
17. Bockus, Henry L. Gastro-Enterology, vol. 11. p. 115. Philadelphia, 1943. W. B. Saunders Co.
18. Warthin, T. A., Warren, R. and Wissing, E. G. Combined medical and surgical management of upper gastro-intestinal hemorrhage. *New England J. Med.*, 241: 473, 1949.
19. Heuer, G. J. Surgical aspects of hemorrhage from peptic ulcer. *New England J. Med.*, 235: 777–783, 1946.
20. Hoerr, S. O., Dunphy, J. E. and Gray, S. J. Place of surgery in emergency treatment of acute massive, upper gastrointestinal hemorrhage. *Surg., Gynec. & Obst.*, 87: 338–342, 1948.
21. Zamcheck, N., Chalmers, T. C., Ritvo, M. and Osborne, M. P. Early diagnosis in massive gastro-intestinal hemorrhage. *J. A. M. A.*, 148: 504–507, 1952.
22. Zamcheck, N., Chalmers, T. C., Ritvo, M. and Osborne, M. P. Fatal gastrointestinal hemorrhage: clinico-pathologic correlations in 101 patients. *Am. J. Clin. Path.*, in press.

Blood Levels after Tracer Doses of Radioactive Iodine in the Diagnosis of Thyroid Disorders*

SOLOMON SILVER, M.D., MACK H. FIEBER, M.D. *and* STEPHEN B. YOHALEM, M.D.
New York, New York

SINCE the introduction by Hertz and his co-workers[1] in 1938 of radioactive iodine as an "indicator in the study of thyroid physiology" numerous attempts have been made to apply these isotopes to aid the clinician in the diagnosis of thyroid disorders as they are seen in his daily practice. That these studies have proved valuable is confirmed by the fact that observations using I^{131} have become routine procedures in the clinical and experimental study of thyroid function.

For the most part these studies have had as their basis the unique concentrating power of the thyroid gland for inorganic iodide so clearly demonstrated by David Marine.[2] It was established very early in the investigations that the increased activity of the hyperplastic, hyperfunctioning thyroid gland in Graves' disease fixed a larger proportion of a tracer dose of radioactive iodine than did the normally functioning gland and that the normal gland surpassed the hypofunctioning organ in this respect. Some observers were not convinced that reproducible, significant values could be obtained by uptake measurements *in vivo* because of the uncertain spatial relationship between the thyroid and the counting tube. They therefore preferred to measure the amount of the isotope excreted in the urine which could be measured with precision and which bore a reverse ratio to that fixed by the gland. There is no doubt that both of these methods are valuable in the diagnosis of hyperthyroidism and the number of reports attesting to their usefulness is constantly increasing.

However, every observer who has worked with these methods has found inexplicable examples of discordant results and has encountered an overlap between the normals and the hyperthyroids that has reduced the value of the method in its clinical application.

Hertz and his co-workers[3] realized in 1949 that a better index of thyroid function could be obtained if one could study the conversion of the administered inorganic iodide into protein-bound iodine because that is the essential function of the thyroid gland and, within limits,[4] no conversion into protein-bound iodine *in vivo* occurs except in the presence of functioning thyroid tissue. They studied the appearance of protein-bound iodine in the plasma of euthyroid and hyperthyroid patients twenty-four hours after tracer doses and concluded that hyperthyroids showed a tendency toward an increased amount of protein-bound I^{131} in the plasma. These workers were restricted because of the low sensitivity of the counting systems available at that time and they failed to prolong their observations beyond twenty-four hours to the time period when significant changes occur. In 1949 Clark[5] repeated these studies but again was handicapped by low sensitivity counters and had to use large tracer doses (500 to 800 microcuries) and also terminated his studies at twenty-four hours after the tracer dose. They also encountered considerable overlap among their hyperthyroid, euthyroid and hypothyroid subjects.

When counters of very high sensitivity such as the windowless Q-gas counter became available, we began our observations using safe tracer doses of 100 microcuries and extending the observations for a longer period of time. This study is an attempt to resolve some of the difficulties previously encountered.

* From the Physics Laboratory and the Medical Service of the Mount Sinai Hospital, New York, N. Y. The I^{131} used in this study was supplied on allocation by the U. S. Atomic Energy Commission.

METHODS

In the first series of observations[7] a group of thirty controls and twenty-four undoubted cases of active hyperthyroidism was selected from the wards of the hospital. The controls were adult patients of both sexes who presented no clinical or laboratory evidences of thyroid disease. The hyperthyroids were all obvious examples of this disorder with increased basal metabolic rates and elevated protein-bound blood iodine values and in whom the diagnosis was accepted by at least three competent clinicians. A tracer dose of 100 microcuries of carrier-free I^{131} was administered intramuscularly in a small volume of sterile saline solution. Blood samples were drawn at frequent intervals and the radioactivity of the whole blood, plasma and the washed plasma proteins was determined in a Q-gas counter (Model D-42*). For counting whole blood, 1 ml. of blood was placed in a suitable planchette, hemolyzed with saponin, to which a drop of 10 per cent NaOH was added. The planchettes were air dried and counted. Plasma was treated in the same manner but no saponin was used. To determine the radioactivity of the protein-bound I^{131} 1 ml. of plasma was added to 2 ml. of 10 per cent trichloroacetic acid and made up to 15 ml. in a centrifuge tube with water. This was mixed and centrifuged. The supernatant fluid was removed and the precipitate washed twice with 15 ml. portions of the diluted trichloroacetic acid. The final precipitate was redissolved in 1 M Na_2CO_3 and brought to a final volume of 2 ml. One milliliter of this solution was placed in a planchette, dried as before and counted. Control experiments showed that this procedure completely removed larger amounts of inorganic I^{131} than could be encountered in this study.

A study of these data showed that significant results were obtained from forty-eight to ninety-six hours after the tracer dose. Therefore, in subsequent studies only a single blood sample was drawn at seventy-two hours after the tracer dose. It was also found that for this determination the oral administration of the I^{131} was just as satisfactory as its parenteral use and this simplified procedure was employed. The use of a single blood sample and the simplicity of the measuring technic make the application of this method practical for every day use.

* Obtainable from the Nuclear Instrument Co., Chicago, Ill.

Our results are recorded as net counts per second per milliliter of blood or plasma with a correction for decay to the beginning of the experiment. Correction for self-absorption has not been included but it has been found to be reasonably constant and to average 72 per cent absorbed for whole blood, 55 per cent for whole plasma and 51 per cent for precipitated plasma. In plasma there was no significant change in self-absorption when the protein concentration varied between 7 and 4 per cent. To convert our "net counts per second per milliliter" to absolute values in microcuries the following formula can be used:

$$\text{Microcuries/ml.} = \frac{\text{“corr. net counts/sec”} \times \dfrac{100}{100 - \%\ \text{self-absorbed}}}{27{,}000}$$

in which 27,000 represents the counts per second per microcurie of I^{131} using the counter we employed. In whole blood one count per second per milliliter is equivalent to .00013 microcuries I^{131}.

RESULTS

Figure 1 shows the degree of radioactivity in 1 ml. of whole blood at various times after the tracer dose of I^{131} administered intramuscularly. It will be seen that in the euthyroid patients there is a steady fall in radioactivity after the administration of the I^{131}. This is due to the fact that the I^{131} is being removed from the circulation by the thyroid gland and is being excreted by the kidneys. Apparently the amount of I^{131} being returned to the circulation as protein-bound I^{131} is not sufficient in the euthyroid subjects to interrupt this decline. In the hyperthyroid patients, however, a striking difference is apparent. The levels reached in the blood during the first eight hours are somewhat less than in the controls, probably due to the fact that the hyperfunctioning thyroid gland is extracting a larger amount of I^{131} from the circulation. At about the eighth hour a remarkable change occurs. The curve of radioactivity reverses its direction and begins to ascend and reaches a plateau between the forty-eighth and ninety-sixth hour. Not only is this so but also the curves separate to such a degree that there is no overlap and the *lowest* values for the hyperthyroids exceeded the *highest* values for the con-

trols from the forty-eighth to the ninety-sixth hour in this series of fifty-four cases.

Table I demonstrates that the high values at forty-eight hours and beyond in the hyperthyroid patients are due to the presence in the plasma of protein-bound I^{131}, presumably secreted into the circulation by the thyroid gland.

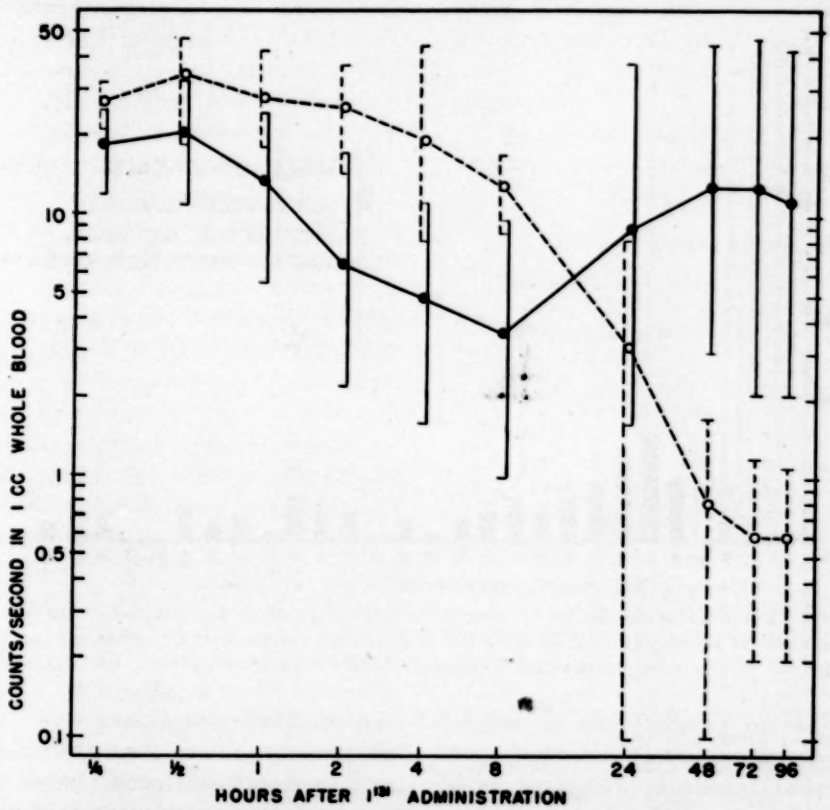


FIG. 1. Activity in whole blood after 100 microcuries I^{131} without carrier; administered intramuscularly. Dots and solid line: hyperthyroids (thirty cases). Circles and broken lines: euthyroids (twenty-four cases). Counts are net counts above background and calculated for decay to time of administration. The range of observed values is indicated for each time period. One count per second is equivalent to 0.00013 microcuries I^{131}.

There is an obvious additional possible cause for high radioactivity of the whole plasma, namely, the retention of inorganic I^{131} due to failure to excrete this substance because of impaired renal function on a renal or "prerenal" basis. That such a situation actually is encountered can be seen from the data in Table II, summarizing results of a study made in a group of seven euthyroid patients with impaired renal function as manifested by albuminuria, elevated blood urea and decreased concentrating power of the kidneys. In all of these it could be shown the high levels of radioactivity were due to retained inorganic I^{131} and that the values for protein-bound (hormone) I^{131} were in the euthyroid range.

At this point it was decided to simplify the procedure because it became apparent that a single blood specimen drawn at seventy-two hours after the tracer dose should give diagnostic information if the total radioactivity of 1 ml. of plasma and the radioactivity of the protein fraction were determined. It was also found that the tracer dose could be administered

TABLE I*

Hours after Injection:	4	24	48	72	96
Euthyroids					
Mean	1.6	1.2	1.4	1.6	1.4
Range	0.6–3	1.0–2	0.4–1.8	1.0–2	0.8–2.2
Hyperthyroids					
Mean	3.0	14.4	22.4	20.6	22.0
Range	1.0–4	2.6–73	5.6–83.4	5.4–73.6	6.0–77.8

* Counts per second due to protein-bound I^{131} per ml. of plasma in normals and hyperthyroids after 100 microcuries I^{131} intramuscularly.

orally without altering the results at seventy-two hours after the tracer dose which remained 100 microcuries of I^{131} without carrier.

We are able to report on 310 successive determinations. As we extended our observations, the absence of overlap between the euthyroid and hyperthyroid patients was no longer absolute; but a diagnostic procedure that gave only three aberrant results in 310 patients is obviously of adequate specificity.

In Figure 2 we present the data on the 310 patients studied.

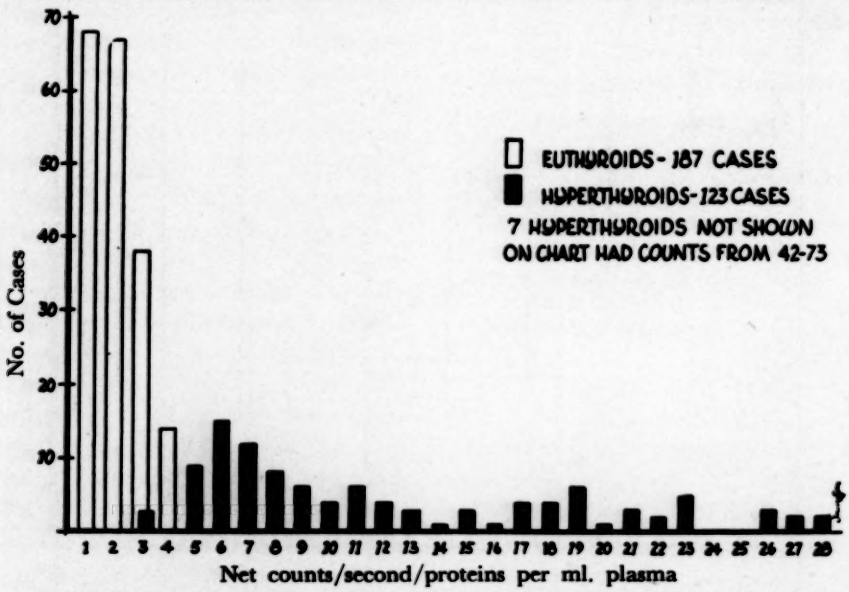

EUTHYROIDS - 187 CASES
HYPERTHYROIDS - 123 CASES
7 HYPERTHYROIDS NOT SHOWN ON CHART HAD COUNTS FROM 42-73
No. of Cases
Net counts/second/proteins per ml. plasma

FIG. 2. Values in net counts per second of washed proteins derived from 1 ml. of plasma at seventy-two hours after 100 microcuries carrier-free I^{131} administered orally. Four counts per second is equal to 0.0003 microcuries I^{131}.

TABLE II *

Hours after Injection:	4	24	48	72	96
Whole blood					
Mean	26.8	17.3	14.0	7.4	5.0
Range	12.6–44.9	5.1–37.0	2.8–27.2	2.9–20.2	0.2–2.6
Plasma					
Mean	53.0	32.4	27.2	13.1	8.7
Range	23.1–81.2	13.2–71.7	6.4–48.4	6.1–31.9	0.6–26.3
Protein-bound Fraction of Plasma					
Mean	1.4	1.4	1.6	0.8	1.6
Range	1.0–1.8	1.0–1.8	1.0–2.2	0.6–1.4	0.8–2.0

* Counts per second per ml. of whole blood, plasma and protein-bound plasma I^{131} after 100 microcuries I^{131} intramuscularly in euthyroid patients with impaired renal function (7 cases).

It is apparent that if the count in the whole plasma is low, less than 4 per second, the values are in the euthyroid range and the determination of the protein-bound I^{131} is unnecessary as it is obviously also less than 4 and therefore falls in the same category. However, high values in the whole plasma must always be checked by a determination of the protein-bound I^{131} as serious errors will occur unless this precaution is taken. The assumption that all the inorganic I^{131} has been removed from the plasma because there is no clinical evidence of renal or "prerenal" disease is unjustified by our experience. Although it is true that obvious renal disease will give a high value for circulating inorganic I^{131} at seventy-two hours, we have encountered similar levels in patients with no obvious renal or cardiac disease. The test depends for its validity on the concentration of protein-bound I^{131} alone and no additional information has been obtained by attempting to use the ratio of inorganic to protein-bound I^{131}.

The value of this test, as with all other tests of thyroid function using I^{131}, is destroyed if iodine-containing compounds or antithyroid drugs such as the thiouracil series have been administered. These drugs pervert the very mechanism which we are trying to measure, namely, the rate of formation and liberation of protein-bound (hormonal) iodine.

On theoretic grounds there is an objection to

the premise on which this method is based, namely, that we are measuring the rate of delivery of thyroid hormone to the circulation. It is apparent that we are not labelling the entire pool of thyroid hormone but only the hormone that is synthesized and liberated *after* the I^{131} has been administered. Previously stored hormone is not labelled and obviously could not be measured by this method. The observed results indicate that this objection is theoretic rather than real and does not interfere with the test because the amount of stored, unlabelled hormone in the hyperplastic gland of Graves' disease is usually very small. This is certainly true in the typical smooth goiter with hyperthyroidism. In toxic nodular goiter it is not uncommon to find areas containing significant amounts of colloid. It has always been suspected that these areas are not highly active and radioautograph studies have confirmed this view. Because of their relative inactivity they apparently do not deliver significant amounts of their stored colloid to the circulation and do not disturb the diagnostic value of this test which has proved equally valuable in the diagnosis of hyperthyroidism with smooth or nodular goiters.

These observations do not help to determine the exact form in which the thyroid hormone circulates. It is now generally accepted that all, or practically all, of the normally circulating blood iodine is bound to plasma protein in a form that resists dialysis and is precipitated by the usual protein precipitants. Earlier studies[8] have shown that not only the globulins but also the albumin of the plasma are iodinated. More recently we[9] have confirmed this by electrophoretic studies using tracer technics with I^{131}. Lebond[10] and his associates have shown by paper chromatography using I^{131} that monoiodotyrosin, di-iodotyrosin and thyroxin normally circulate loosely bound to protein but can be separated from the protein carrier by extraction with butyl alcohol.

SUMMARY

A method employing safe tracer doses of I^{131} and a sensitive windowless counter is described which permits measurement of the total and protein-bound radioactivity in 1 ml. of plasma seventy-two hours after oral administration of the tracer dose.

The results in a series of 187 euthyroid and 123 hyperthyroid subjects are presented. In these 310 cases only three discordant values were encountered, results better than were obtained with any other test for hyperthyroidism employed.

The method requires the use of a windowless counter or counter of similar sensitivity but if this is available the technic is simple and specific.

REFERENCES

1. Hertz, S., Roberts, A. and Evans, R. D. Radioactive iodine as an indicator in the study of thyroid physiology. *Proc. Soc. Exper. Biol. & Med.*, 38: 510, 1938.
2. Marine, D. and Rogoff, J. M. How rapidly does the intact thyroid gland elaborate its specific iodine-containing hormone? *J. Pharmacol.*, 9: 1, 1917.
3. Freedberg, A. S., Ureles, A. and Hertz, S. The serum level of protein-bound radioactive iodine in the diagnosis of hyperthyroidism. *Proc. Soc. Exper. Biol. & Med.*, 70: 679, 1949.
4. Morton, M. E., Chaikoff, I. L., Reinhardt, W. O. and Anderson, E. Radioactive iodine as an indicator of the metabolism of iodine. *J. Biol. Chem.*, 147: 757, 1943.
5. Clark, D. E., Moe, R. H. and Adams, E. E. The rate of conversion of administered inorganic radioactive iodine into protein-bound iodine of the plasma as an aid in the evaluation of thyroid function. *Surgery*, 26: 331, 1949.
6. Williams, R. H., Jaffe, H. and Bernstein, B. Comparison of the distribution of radioactive iodine in serum and urine in different levels of thyroid function. *J. Clin. Investigation*, 28: 1222, 1949.
7. Silver, S. and Fieber, M. H. Blood levels of I-131 after tracer doses in the diagnosis of hyperthyroidism. *Proc. Soc. Exper. Biol. & Med.*, 75: 570, 1950.
8. Silver, S. Nature of the blood iodine. II. Nature of the plasma iodine. *Proc. Soc. Exper. Biol. & Med.*, 46: 213, 1941.
9. Silver, S. and Reiner, M. The distribution of the protein-bound iodine in the electrophoretic fractions of human serum studied with radioactive iodine. *Bull. New York Acad. Med.*, 26: 277, 1950.
10. Gross, J., Lebond, C. P., Franklin, A. E. and Quartel, J. H. Presence of iodinated amino acids in unhydrolyzed thyroid and plasma. *Science*, 111: 605, 1950.

Reviews

Protein Flocculation Reactions*

A Physico-chemical Approach

ABRAHAM SAIFER

Brooklyn, New York

THE term "protein flocculation reaction" covers a whole series of reactions of proteins with diverse cationic or anionic substances in which a colloidal suspension, flocculate or precipitate is formed by certain protein fractions and inhibited by others. The increasing importance of this field is evidenced by the fact that one of the most recent texts of protein chemistry, that of Haurowitz,[1] devotes two paragraphs to a description of flocculation reactions; and that, for the first time, they have been given separate treatment as a group in a review article in the Annual Reviews of Biochemistry.[2]

It is unfortunate that a field of protein chemistry which has been shown to have such useful clinical applications to both diagnosis and treatment in disease has received so little attention from the biochemical point of view. Application of quantitative biochemical technics to the mechanisms of these flocculation reactions might well give important information concerning the functions and origins of the body proteins and might have immediate application to the study and treatment of certain infectious and chronic diseases.[3] The purpose of this review is to collect and correlate the available data in order to assess the information now at hand.

DESCRIPTION OF TYPICAL PROTEIN FLOCCULATION REACTIONS

Three of the most widely used serum protein flocculation tests are the cephalin-cholesterol flocculation reaction of Hanger,[4] the thymol turbidity and flocculation reaction of Maclagan[5] and Neefe,[6] and the zinc turbidity reaction of Kunkel.[7] Since each of these tests is somewhat different in principle and each is typical of a host of other similar flocculation tests, they will be discussed in some detail, with only brief mention of the other tests which fall in the same category.

Cephalin-cholesterol Flocculation Reaction. The cephalin-cholesterol emulsion is prepared by the evaporation of an ether solution of cephalin-cholesterol from water at 65 to 70°C. and a one-sixth reduction in the volume of water by evaporation just below the boiling point. One milliliter of this emulsion is added to 4 ml. of a 1:20 dilution of fresh sera with 0.85 per cent saline. The mixed contents are allowed to stand at room temperature in a dark cabinet for twenty-four to forty-eight hours. A saline blank and known normal and abnormal sera are run simultaneously with each set of unknowns. The degree of flocculation is read qualitatively as from 0 to 4+ at these time intervals. A reading of 1+ or greater at twenty-four hours is considered abnormal.

Thymol Turbidity Test. The thymol reagent consists of a saturated solution of thymol in a barbiturate buffer at pH 7.6 to 7.7. To 0.1 ml. of serum is added 6 ml. of the thymol buffer in a colorimeter tube. The contents are mixed and allowed to stand for thirty minutes. The degree of turbidity is read in a photoelectric colorimeter at 660 mμ against thymol buffer as a blank. The unknowns are compared against a curve of varying $BaSO_4$ turbidities and the results expressed *semi-quantitatively* in turbidity units. For human sera a value from 0 to 4 Shank-Hoagland units[8] which is equivalent to 0 to 2 Maclagan units[9] is considered normal.

For the thymol flocculation reaction the tubes from the thymol turbidity test are allowed to stand in a dark cabinet for twenty-four and forty-eight hours and the degree of flocculation is read *qualitatively* from 0 to 4+.

* From the Biochemistry Department of the Division of Laboratories, Jewish Sanatorium and Hospital for Chronic Diseases, Brooklyn, N. Y.

Zinc Flocculation Method. The solution used in this procedure contains 24 mg. per L. of $ZnSO_4.7H_2O$ in barbiturate buffer at pH 7.5. To 0.1 ml. of serum is added 6 ml. of the buffered $ZnSO_4$ reagent in a colorimeter tube. The contents are mixed and allowed to stand for thirty minutes. The turbidity is read in a photoelectric colorimeter at 650 mμ against the buffered $ZnSO_4$ solution as a blank. The turbidity readings are transferred into units by the use of a standard curve similar to the one employed for the thymol turbidity test. The normal range for this method is from 2 to 12 units.

OTHER PROTEIN FLOCCULATION REACTIONS

Category of the Cephalin-cholesterol Flocculation Reaction. The cephalin-cholesterol flocculation reaction is illustrative of a large number of similar reactions employed for detecting changes in the protein composition of biologic fluids. In these tests a charged colloidal suspension is flocculated out of solution by a change in charge distribution of the proteins in the fluid being tested as compared to those present in normal fluid. Examples are the colloidal gold reaction of Lange[10] for cerebrospinal fluid, which has been applied to serum proteins by Gray[11] and Maclagan;[12] the colloidal mastic test of Emanuel[13] and the colloidal benzoin test of Guillain,[14] both of which have been applied to the sera in liver disease by Fischer and Wiltner;[15] the colloidal scarlet red test of Maizels[16] as modified by Ducci[17] also gives positive flocculation reactions in liver disease. The cephalin-cholesterol flocculation reaction first applied to sera has been modified for use with cerebrospinal fluid by Saifer.[18]

Category of the Thymol Turbidity Test. This reaction is illustrative of a number of flocculation reactions in which a turbidity or precipitate is formed with organic compounds containing phenolic linkages or other acidic, basic or strongly polar groups when added to certain protein fractions. Included in this category is the well known Pandy test for globulin in cerebrospinal fluid which is based upon the reaction of a saturated solution of phenol with increased globulins. In addition many organic acids, for example trichloracetic acid, p-toluene sulfonic acid and acetic acid, are routinely employed as protein-precipitating agents.

Polar compounds which produce protein precipitation by neutralization of the charged field surrounding the colloidal particles would include water, alcohol, acetone, salts and so forth. Dilution of the concentrated proteins present in biologic fluids by solvents with weak polar groups, for example, water, will serve to decrease the charge density on the protein molecules. In addition to this dilution effect, desolvating agents such as alcohol and concentrated salt solutions will convert solvated particles into lyophobic systems by removal of water from the surface of the protein molecules.

For example, as shown by Wiseman[19] and by Dreyfuss[20] serum proteins in certain diseases can be flocculated simply by the addition of water. A similar turbidity test based upon dilution of sera with 15 per cent alcohol was proposed by Love and Mawson[21] for jaundiced sera. Still another dilution type test was published by Naumann[22] who employs water saturated with CO_2. Use is made of the well known reaction between proteins and formaldehyde in the formol-gel test of Gaté and Papacostas,[23] as modified by Wise and Gutman,[24] in which abnormal sera show increased viscosity or gelation under standardized conditions while normal sera do not. As suggested by Gutman[25] the formol-gel reaction is not a typical protein flocculation reaction but involves the formation of cross links between reactive groups of different protein molecules by the action of methylene groups derived from formaldehyde. Although it is difficult to draw a sharp dividing line, such reactions, as well as reactions involving protein precipitation with concentrated salt solutions, are excluded from this discussion of protein flocculation reactions in the strict sense of the term.

In recent months a number of papers have appeared in the literature involving the use of cationic detergents as protein flocculating reagents. Jacox,[26] and Jacox and Gale[27] have employed the quaternary ammonium salt, octab. This reagent reacts with diluted sera at pH 6.8 to give turbidities which can be measured in a photometer. The reactivity has been found to reside in the globulin fraction, is markedly increased in many chronic diseases and can be used as a convenient method for estimating inflammatory activity during the course of rheumatic fever.[27] A similar protein flocculation reaction using a cationic detergent of the quaternary ammonium salt type, for example, bradasol, has been described in a paper by Mayer and Eisman[28] and its clinical evaluation in cases of malignancy given in a companion

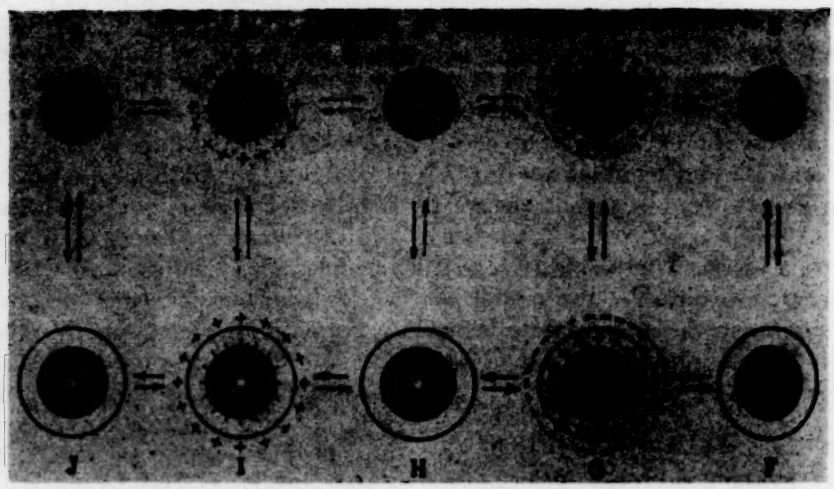


FIG. 1. A diagrammatic representation of the relationships which exist between the solvation of a particle and the electrical charge of a particle, showing that both are important as factors influencing stability. A to E are lyophobic particles of which only B and D will exist in stable sols. F to J are lyophilic particles. All will be relatively stable as contrasted to the lyophobic series but G and I have two factors for stability, solvation and electric charge. Suitable electrolytes in low concentration will neutralize or even reverse the charges. "Desolvating" agents (e.g., alcohol for water systems) will convert the solvated particles to lyophobic systems. (From Gortner and Gortner[38] after Bungenberg de Jong.)

paper by Bronfin and his co-workers.[29] Since these reagents are complex organic molecules with highly charged polar groups, their interaction with proteins to produce turbidities is not surprising.

Category of the Zinc Flocculation Method. This method is basically an interaction of a protein with a divalent metal ion, for example, Zn^{++}, and is thus illustrative of many similar reactions which have been employed in detecting changes in the protein composition of sera in disease. An example of such flocculation tests is the Takata-Ara reaction[30] upon which depends the reaction of proteins with a colloidal solution of mercuric oxides formed from mercuric chloride and sodium carbonate. Modifications of this reaction have been published by Jezler,[31] Magath[32] and Wayburn and Cherry.[33] Another test based upon the reaction of metallic ions with proteins is the cadmium sulfate reaction of Wunderly and Wuhrmann[34,35] which is popular in European laboratories. Another mercuric salt reaction involves use of Hayem's solution which contains both mercuric chloride and sodium sulfate. This test was first described by Gros[36] and has been further modified by Mandel, Paris and Harris.[37]

Other divalent or trivalent metallic ions could be employed in developing similar tests. For example, in Kunkel's original paper on the zinc flocculation reaction[7] similar data are given for copper sulfate solutions.

MECHANISM OF PROTEIN FLOCCULATION REACTIONS

General

Most proteins in solution consist of colloidal particles from 10 to 1,000 Å in size. Most are lyophilic and are stabilized both by an electric double layer and by solvation in the region of the interface with the medium of dispersion. Lyophobic colloids, although possessing a lesser degree of stability, can also become more stable in the presence of a charged field. Neutralization of the charged field, particularly by bringing the pH to the vicinity of the isoelectric point by addition of small amounts of di- or trivalent electrolytes, influences only the electrokinetic potential on the micelle. Flocculation of lyophobic colloids will then take place. The addition of *larger* quantities of electrolytes influences the degree of solvation and causes flocculation to occur in lyophilic colloids.

These phenomena are illustrated diagrammatically in Figure 1 which is taken from the recent text by Gortner and Gortner.[38]

Since protein solutions remain stable for long periods of time, it must be assumed that the forces of repulsion existing between the particles

are greater than the forces of attraction, and as a result the individual particles never approach each other closely enough or do not remain together at the point of their closest approach. In lyophobic colloid systems it is the electrical forces resulting from the existence of the double layer of ions in the region of the interface that constitute the stabilizing forces of repulsion. It is generally assumed that if in spite of all repelling forces two lyophobic particles should be made to approach each other, attracting forces (for example, interfacial tension forces, von der Waals-London forces) would come into play to hold them together. As this process continues, flocculation results. It is also generally assumed that the forces which in an unstable sol bring about this required close approach arise from the kinetic motion of the particles. If, then, the maximum kinetic energy of approach attainable by any two particles in a sol is less than the electrical energy absorbed as a result of distortion of their double layers during their approach, movement toward each other will stop short of the distance at which the attracting forces are great enough to maintain them in a state of combination strong enough to cause permanent coherence. Since most of the protein flocculation reactions to be discussed in this paper are not due to protein-protein interactions but rather due to the interaction of proteins with ions, dyes, emulsions, lipids, organic polar groups and so forth, it should be emphasized that such interactions also occur most readily when the potential across the electrical double layer has been reduced to a minimum.

Hardy,[39] Ellis[40] and Powis,[41] among others, early considered the magnitude of the stability factor, and hence the electrical energy involved in this process, to be proportional to the electrokinetic potential.

Helmholtz[42] in 1879 first developed the equation of the electrical double layer from the theory of the condenser, as follows:

$$1. \qquad \zeta = \frac{4\pi d\sigma}{D}$$

where:

ζ = potential difference between the layers
σ = charge density on unit area of layer
d = distance between layers
D = dielectric constant of medium existing between the layers.

Gouy[43] in 1910 and later Freundlich[44] pointed out that d must be variable with electrolyte content of the system and that the outer sheet of the double layer must be regarded as a diffuse layer. d must be interpreted as the distance between the "fixed" layer and a plane containing the "electrical center of gravity" of the diffuse layer. The relationship between the older Helmholtz electric double layer theory and the more modern concepts of Gouy and Freundlich is shown graphically in Figure 2, taken from a recent paper by Hauser.[45] In a recent review article dealing with modern colloid-chemical concepts of the phenomena of coagulation Hauser[45] points out that in addition to the older concepts of charge and solvation as stabilizing factors modern theory must take into account that ions located at a surface are chemically unsaturated as compared with those located in the interior. These ions can undergo reactions with other ions present in the solvent and the ability of these latter ions to undergo solvation will determine the stability of a colloid. Many surface phenomena exhibited by colloids can also be explained on the basis of principles which govern the atomic structure of crystals, for example, siliceous matter.

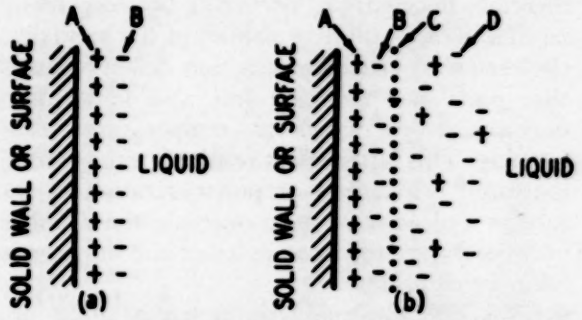


FIG. 2. Electric double layers: (*a*) Helmholtz; (*b*) Gouy-Freundlich. A, charges firmly attached to particle; *Ba*, charges in liquid layer; *Bb*, ions in liquid layer firmly attached to particle; C, thickness of attached layer; D, diffuse ions in movable part of liquid. (The particle plus *Ab* and *Bb* is the colloidal micelle.) (From Hauser.[45])

In the foregoing equation ζ applies only to a given sol at a given temperature. Such factors as increased dielectric constant, decrease of charge density of sol and decreased distance between layers will decrease the electrokinetic potential and therefore reduce the stability of the sol. However, the process of flocculation is a more complex phenomenon than indicated by the equation and often produces completely divergent results as the various interweaving factors come into play and assume greater or

lesser importance. Some of these factors are as follows:

Temperature. It is expected that increasing the temperature of a colloidal system will serve to increase the kinetic energy of the charged particles and the possibility of collisions (and therefore flocculation) occurring between them. In making quantitative studies of the cephalin-cholesterol flocculation reaction Saifer[46] found that such was the case but also found that flocculation increased at temperatures near freezing. This latter effect resulted perhaps from increased orientation or polymerization of the solvent molecules so as to decrease the distance between layers (d) or to increase the number of effective collisions.

pH. The electrokinetic potential does not have to drop to zero before the sol becomes unstable; there is a critical pH zone in the vicinity of the isoelectric point where the magnitude of the potential is not sufficiently great to insure indefinite stability. The simplest way to decrease charge density (σ) is to bring the pH of the sol to the vicinity of the isoelectric point.

Dilution. Saifer[47] found that, other factors remaining constant, the effect of dilution was to increase flocculation in the cephalin-cholesterol flocculation reaction. Since from x-ray diffraction studies the protein molecule is believed to unfold in more dilute solutions, the decreased stability might be due to a marked decrease in charge density per unit surface area although the actual total number of charged groups in the surface may increase with dilution. This would explain why most flocculation reactions take place best in solutions of low ionic strength.

Changes in Distance between Layers (d). It is generally assumed that electrolytes added to colloid systems, particularly in the vicinity of the isoelectric point, reduce the electric charge to near zero and cause the particles to flocculate. However, if the Gouy-Freundlich diffuse layer theory is taken into consideration, the energy of the electric field can be altered by a change either in the density of the charge or in the distance which separates charges of opposite sign. The addition of electrolytes more often than not causes an increase in charge but causes d to decrease so greatly that the electrokinetic potential decreases. At a critically low value of this potential the colloid flocculates. Gouy calculated that a surface in contact with 0.1 N NaCl, d = 0.96 mμ; for .001 N NaCl, d = 9.6 mμ; for pure H_2O, d = 1010 mμ. This would explain why globulins are soluble in dilute NaCl, even at pH levels near the isoelectric point, due to an increase in charge, but flocculate readily with di- or trivalent ions which cause d to decrease markedly.

It is as a result of such experiments with mono- and polyvalent salts that Eilers and Korff[48] have suggested that the factor ζ^2/K (where K = 1/d, and d is the thickness of the electrical double layer) is a more accurate measure of the electrical energy of repulsion which determines stability than is ζ above.

Dielectric Constant and Desolvation. From the foregoing equation it can be seen that reduction of the dielectric constant (D) would increase the stability of the colloid. Since water is a liquid of high dielectric constant, the use of almost any other solvent, for example, alcohol, dioxane, acetone, should serve to stabilize the colloid. Conversely, the addition of amino acids, for example, glycine, increases the value of (D).[49] In practice, addition of organic solvents generally serves to precipitate protein solutions. Since most naturally occurring proteins are lyophilic in nature, the explanation for this must be sought in the "desolvation" effect of these substances on such colloids or in the increased effectiveness of collisions in media of low dielectric constant. Concentrated salt solutions containing monovalent cations, for example, sodium sulfate, sodium sulfite, also exert their precipitating action through such a mechanism. This is illustrated in Figure 1.

Selective Absorption of Ions. Michaelis[50] noted that such substances as cellulose, collodion and hydrocarbons, which have no tendency toward dissociation or toward oriented absorption, are negatively charged. Michaelis assumed that OH^- ions are more capillary-active than H^+ ions, so that the surface of the disperse phase would have a greater concentration of OH^- carrying a negative charge. Negatively charged ions are, in general, less hydrated than positively charged ions, for example, $H_3{}^+O$. Less work is required for them to move into the region of the interface. Hence non-ionogenic surfaces such as cephalin-cholesterol emulsion, dyes, gum mastic and colloidal benzoin are usually negatively charged in relation to water.

Relation of Mechanism to Electrophoretic Studies of Protein Fractions

Even before the advent of the Tiselius electrophoresis apparatus it was recognized by many observers that while the albumin-globulin ratio,

as determined by the classical salt precipitation methods, may remain within normal limits changes in both the albumin and globulin fractions may occur in many diseases. In liver diseases, particularly, there is a decrease in the albumin fraction together with a marked increase in the globulin fraction, especially in the gamma globulin.[57] (Fig. 3.) It is in just such disorders that positive protein flocculation reactions are found.

The mechanism of a number of the more commonly used flocculation reactions has been studied by determining which electrophoretic fractions are involved in the reaction, either as active components or as inhibitors. One of the earliest workers using this approach was Gray,[53,54] who performed a series of electrophoretic studies on the sera of all types of liver diseases. These studies revealed that the most consistent and characteristic alteration of the serum proteins was an increase in the gamma globulin, associated with a decrease in albumin. Gray[54] then studied the effect on the colloidal gold reaction of the addition of purified protein fractions to normal serum and found that: (1) the addition of pure gamma globulin to normal blood serum gave a positive colloidal gold reaction, (2) alpha and beta fractions had no effect and (3) the albumin fraction inhibited the colloidal gold reaction. The colloidal gold reaction was also studied in this way by Kabat and his co-workers[55] who obtained similar results. Alpha and beta globulins were reported by Maclagan and Bunn[56] to be more inhibitory than albumin for this reaction.

The mechanism of the widely used cephalin-cholesterol flocculation reaction of Hanger was studied from the electrophoretic viewpoint in series of papers by Kabat et al.,[57] Moore and co-workers,[58] Hanger[59] and Maclagan and Bunn.[60] A positive reaction is attributed to one or more of the following conditions: (1) increase of gamma globulin in such quantity that the normal components of the serum albumin fraction are unable to inhibit the reaction; according to Hanger[59] this is the case in certain non-hepatic disorders; (2) decrease in serum albumin concentration below that capable of inhibiting the reaction, for example, cirrhosis; (3) decrease in flocculation-inhibiting properties of the serum albumin fraction due to its chemical modification, as in viral hepatitis according to Hanger.[59]

Maclagan and Bunn[60] have shown that the gamma globulin fraction obtained from hepatitis sera is a more potent flocculating agent than is normal gamma globulin and that alpha and beta globulins from hepatitis sera show flocculating properties. Moore et al.[58] had previously shown that albumin from hepatitis serum had less inhibitory power than albumin from normal serum: normal serum albumin inhibited flocculation of normal gamma globulin when the ratio of albumin to gamma globulin was 20:1 whereas hepatitis albumin in this ratio reduced the flocculation only from 4+ to 3+. Maclagan and Bunn[60] found that a 100:1 ratio of albumin to gamma globulin was required for such inhibition. Minor differences in the separation of protein components may explain the divergent results, as gamma globulin separated at pH 8.5 (barbital buffer) did not flocculate with the cephalin-cholesterol emulsion while that separated at pH 7.4 (phosphate buffer) did.

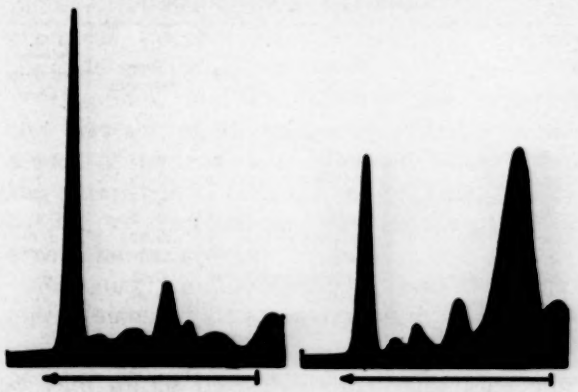


FIG. 3. Ascending electrophoretic patterns for normal serum (A) and cirrhosis serum (B). The large peak on the right is gamma globulin whose concentration in this case exceeds that of albumin in the normal serum; the area under the albumin peak (at extreme left) is approximately equal to all the areas under the various globulin peaks added together. (From Kunkel et al.[52])

The thymol turbidity reaction of Maclagan[5] appears to involve a mechanism fundamentally different from that of the cephalin-cholesterol flocculation reaction, according to both clinical[6,61] observations and laboratory[62] observations. Maclagan[63] has implicated a lipid-containing fraction of the serum. Cohen and Thompson[64] found that the thymol reaction precipitates primarily beta globulin from normal or hepatitis sera. The major change in electrophoretic pattern of hepatitis serum following thymol treatment is a 50 per cent reduction in beta globulin as against an average decrease in gamma globulin of about 4 per cent. Although the removal of beta globulin by thymol is much less in normal serum, the precipitate is indistinguishable by electrophoretic or ultracen-

trifugal technics from that of pathologic sera. The beta anomaly always disappears after thymol addition. Recant et al.[62] found no evidence for the presence of an abnormal lipid and suggested that the critical alteration may be non-lipid since ether-extracted serum may be resensitized to thymol by addition of lipid only in previously positive sera.

TABLE I (FROM MACLAGAN[68])

Test	Precipitating Agent	pH	Ionic Strength	Serum Dilution Factor
Takata-Ara	$HgCl_2$	c. 10	0.15	2–16
Formol gel	H.CHO	c. 8	0.15	1
Cephalin cholesterol	C.C. emulsion	c. 8	0.12	26
CdSO	$CdSO_4$	c. 8	0.10	1
Sharlach red	Sharlach red	c. 8	0.075	2–8
Weltmann	$CaCl_2$	c. 8	0.02–0.002	51
Colloidal gold	Colloidal gold	7.8	0.01	61
Thymol	Thymol	7.8	0.01	61
$ZnSO_4$	$ZnSO_4$	7.5	0.002	61

Maclagan[63] and Carter and Maclagan[65] believe the positive thymol turbidity test to be associated with changes in the gamma globulin, together with changes in the phospholipids. Maclagan and Bunn[56] report faint turbidity of pure gamma globulin to thymol and considerable increase in turbidity on addition of cephalin or lecithin. They found the reaction to be inhibited by normal but not by hepatitis albumin. Kunkel and Hoagland[66] take an intermediate view. They find that both lipids and abnormal lipid-protein complexes migrating in the beta globulin fraction of the sera are responsible for a positive test but that the gamma globulin fraction of serum also plays an important role. The relative importance of the different components varies with different sera. Development of turbidity is prevented if the lipids are kept in solution by the addition of a Tween, are extracted with ether or if gamma globulin is removed

The mechanism of the cadmium flocculation reaction of Wuhrmann and Wunderly[34] has been studied by the originators.[67] They found that a positive cadmium reaction is due chiefly to an increase in gamma globulin but also to an increased content of alpha globulin and to a lesser extent of beta globulin and albumin.

An excellent summary of the chemical basis of the more commonly used flocculation tests appeared recently in an article by Maclagan.[68] Table I and Table II, reproduced from this paper, summarize the chemical and electrophoretic data for these tests.

MODIFICATION OF PROTEIN FLOCCULATION TECHNICS TOWARD A MORE QUANTITATIVE APPROACH

On the basis of the general theoretical considerations of the protein flocculations and particularly because of the application of electrophoretic studies, many investigators began working toward a more *quantitative* approach to protein flocculation reactions. Instead of visual observation of the degree of flocculation or use of visual turbidity standards, a number of investigators have proposed the use of spectrophotometric[8] or photoelectric methods[69] or, better still, a photoelectric turbidimeter[70] which responds to light scattering and is independent of color.

Stabilization of the cephalin-cholesterol reagent has presented difficulties. Neefe and Rein-

TABLE II (FROM MACLAGAN[68])

Test	Protein Fractions Active		Correlation with Total Globulin	Diseases in which Most Useful
	Precipitating	Inhibiting		
Thymol	γ-globulin	Albumin	Slight	Hepatitis
Gold	γ "	Albumin α and β globulin	"	Hepatitis, infections
Cephalin cholesterol	(αβ)γ "	Albumin	"	Hepatitis
Takata-Ara	(αβ)γ "	"	"	Liver disease
Formol gel	(αβ)γ "	"	Close	Kala-azar, infections
Weltmann short	αβ "	"	?	Lung infections
" long	γ "	.....	.....	Lung infections
$CdSO_4$	(αβ)γ "	"	?	Infective hepatitis

hold[71] were the first to point out the effect of light and temperature in producing false-positive reactions. Steinberg[72] recommended the use of cholesterol-desoxycholic acid emulsion as a more stable emulsion in place of the cephalin-cholesterol emulsion usually employed in the Hanger test. The use of a bile acid in place of a phospholipid would lend support to the view that the phospholipid acts essentially as an emulsifying agent for the cholesterol which enters into chemical combination with the protein fraction.

Alterations in the apparent proportions of the components of the serum proteins by physical means before measurement electrophoretically or by salt precipitation is well known. A number of investigators[44,73,74] have shown that increasing the range of dilution of sera above the 1:20 dilution usually employed in the cephalin-cholesterol reaction yields positive tests with both normal and abnormal sera. Wunderly and Wuhrman[35] postulate that a binding occurs between gamma globulin and albumin in normal sera in dilutions of less than 1:20 but that in higher dilutions, or in abnormal sera, bonds are broken permitting flocculation to take place with the free gamma globulin. Makari[75–77] has made use of a technic involving serial dilution of sera with saline in conjunction with the cephalin-cholesterol method. Flocculation increases from 0 at the standard dilution of 1:20 to a peak of 3+ to 4+ at 1:400 with decline to 0 again upon dilution to about 1:6,000. Makari postulates an "inhibiting factor" which is diluted out earlier than the "flocculating factor." Frisch and Quilligan[78] have used both serial dilutions and temperature effects, together with a modified cephalin-cholesterol emulsion which is prepared at room temperature and has greater stability and less light sensitivity than the usual emulsion that is prepared at 70 degrees. This dilution factor would explain the almost 100 per cent positive flocculation tests found with ascitic fluid.[79]

Saifer[44] has employed a quantitative cholesterol method for determination of the total cholesterol content of the centrifuged flocculated material obtained in the Hanger test. This work furnishes experimental evidence for the stoichiometric interaction between cholesterol and certain protein fractions, for example, gamma globulin. Since this method can determine slight variations in the amount of flocculated material in terms of quantitative cholesterol units, it has been employed to study such factors as dilution[44] and temperature variation.[43]

Much of the recent work with protein flocculation methods has attempted to develop quantitative procedures which can be related to definite protein fractions separated by either chemical (alcohol precipitation) or electrophoretic methods.

Dauphinee and Campbell[80] have reported the presence of an abnormal globulin in the serum of patients with diseases which affect the parenchymal cells primarily. They employ a 13.5 per cent sodium sulfite solution in their separation procedure.

Although immunochemical and salt precipitation methods are not protein flocculation methods in the strict sense of the term, a large number of such procedures for the determination of various protein fractions in biologic fluids have been published. Of special interest is the procedure of Wolfson, Cohn and their co-workers[81] because it has been applied by Huerga, Popper and their co-workers[82,83] to the estimation of serum gamma globulin concentration by turbidimetry and the results compared with both the zinc sulfate and electrophoretic methods. The turbidity measurements are translated into grams of gamma globulin per 100 ml. of serum by use of the chemical method of Wolfson et al.[81] The turbidity was found to be independent of the albumin and lipid content and recoveries of added gamma globulin by both turbidimetric and chemical methods were about 80 per cent. In a subsequent paper these investigators[83] found that the protein fraction determined turbidimetrically is not identical with electrophoretic gamma globulin. They found an average difference of about 15 per cent between the two procedures but a closer correlation between their turbidity test and electrophoretic results than between the latter and the zinc turbidity test, which is influenced both by albumin and lipids. Although this test is an improvement in the quantitative approach, it still falls short of a reliable chemical method for gamma globulin.

The lack of correlation between electrophoretic determinations of serum gamma globulin and of the previously described protein flocculation tests of Kunkel[7] and of Huerga and Popper,[82] which supposedly measure gamma globulin concentration quantitatively, is reported in a recent paper by Ricketts et al.[84]

This paper reports errors of about 20 per cent for normal sera and as much as 100 per cent for sera in various diseases such as portal or biliary cirrhosis.

That there is a relationship between the flocculating properties of a protein in solution and its electrophoretic mobility can be seen from a comparison of Equation 1, as given previously, with the standard electrophoresis equation:

$$2. \qquad \zeta = \frac{4\pi v\eta}{ED}$$

where: v = velocity of migration
E = the applied e.m.f. per unit length in the cell
η = the viscosity
D = the dielectric constant

It can be seen that both the flocculating property (or stability factor) of a protein solution and its electrophoretic mobility are functions of the zeta potential (ζ) across the double layer. In the electrophoretic method separation of protein fractions carrying different charges is achieved by means of a constant e.m.f. which is applied, whereas separation of protein fractions by flocculation reactions can be achieved by suitable pH variation and controlled changes in the ionic field of the solvent surrounding the charged protein molecules. Such an approach has recently been employed by Saifer and Zymaris[85] for the photometric microdetermination of electrophoretically pure gamma globulin (Cohn's fraction II) in the range of 100 to 1,000 μg. of protein. The method is based on an extension of a previously published method for cerebrospinal fluid[18] in which gamma globulin is precipitated quantitatively from solution by means of a mixture of cephalin-cholesterol emulsion and Hayem's solution. The protein content of the ether-washed complex is determined quantitatively by the ninhydrin method of Moore and Stein.[86] The method has been applied to human sera and compared with the electrophoretic method.[87] Excellent correlation between the two methods was found over a wide range of gamma globulin values, with good reproducibility of results with 0.01 to 0.02 ml. serum and satisfactory recoveries of added gamma globulin.

RELATIONSHIP OF SERUM PROTEIN FLOCCULATION TO CEREBROSPINAL FLUID FLOCCULATION REACTIONS

Kafka and his co-workers[88] showed that in many neurologic disorders such as multiple sclerosis and neurosyphilis changes may occur in the ratio of albumin to the globulins present in the cerebrospinal fluid without significant increase in the total protein values. They identified these increased globulins as euglobulin and fibrinogen. These investigators found on studying the mechanism of the colloidal gold reaction that the color changes are due to an active globulin fraction of the cerebrospinal fluid while the albumin fraction has a protective action.

These findings have been confirmed by the more recent work of Kabat, Moore and Landow[55,89] employing electrophoretic technics. These investigators have shown that the electrophoretic pattern of cerebrospinal fluid proteins resembles that of serum and that alterations in the composition of the protein components of serum are reflected in the cerebrospinal fluid although the changes are not as marked, except for certain neurologic diseases in which changes may be even more marked than in the blood.

The fact that there is a relationship between changes in protein composition of blood sera and cerebrospinal fluid in disease is also shown by the application to blood sera of the colloidal gold test,[11,12] the colloidal benzoin[15] and the shellac test,[15] all of which were originally applied to cerebrospinal fluid. Conversely, the cephalin-cholesterol flocculation reaction has been applied to cerebrospinal fluid[18] as has the thymol turbidity test[90] and the zinc sulfate turbidity test.[91]

A number of investigators have shown that when the concentration of any protein component of the serum for example, an antibody, reaches a concentration 200 times greater than that normally present, the component appears in the cerebrospinal fluid.

CLINICAL ASPECTS OF PROTEIN FLOCCULATION REACTIONS

No attempt will be made in this paper to review the voluminous medical literature dealing with protein flocculation reactions. Instead, recent papers which either review the literature on this subject or are concerned with the relationship of flocculation studies to electrophoretic procedures will be discussed.

Maclagan[68] divides diseases with a relative increase in serum gamma globulin content, namely, positive flocculation reactions, into two general classes: (1) liver diseases—hepatitis,

cirrhosis, chronic passive congestion; he attributes positive flocculation in this category to abnormal protein synthesis in the liver; (2) infectious diseases—bacterial endocarditis, malaria, lymphogranuloma venereum, tuberculosis, certain cases of plasmocytoma, infectious mononucleosis. He suggests that a positive flocculation reaction in this group represents an increase of circulating antibody.

Liver Diseases. An excellent review article on the general subject of serum proteins in hepatic disease has been written by Dauphinee and Campbell.[80] Articles dealing with newer tests for hepatic dysfunction have appeared by Schrumpf,[92] Steigmann et al.,[93] Linder et al.[94] and Klatskin.[95] Protein flocculation tests have proven useful in differentiating between medical and surgical (obstructive) jaundice, particularly when used in conjunction with alkaline phosphatase determinations, according to Gutman and Hanger,[96] Popper and Steigmann,[97] Mawson[98] and others.

Comparative studies of various protein flocculation tests as applied to liver as well as non-hepatic disease have been published by Kibrick and Clements,[99] Dreyfuss,[20] Ernst and Dotti,[100] Strade, Dotti and Ilka,[101] and Oppenheim, Bruger and Frost.[102] The relationship between liver function tests and liver histology has been studied by Franklin and his co-workers[103] and by Mateer and his co-workers.[104] Histologic studies were also carried out by Ricketts et al.[105] in correlations with electrophoretic studies and bromsulfalein retention in asymptomatic portal cirrhosis, with rather inconclusive results.

Rafsky et al.[106] have performed simultaneous liver function tests and chemical and electrophoretic analysis on the sera of forty patients with liver disease. They obtained abnormal results by electrophoretic analysis in cases of cirrhosis and carcinoma of the liver which were in marked contrast to the normal results obtained by chemical methods.

Extensive electrophoretic studies in liver disease employing both plasma and sera have recently been reported by Franklin and his co-workers.[107,108] They report markedly elevated fibrinogen values in the cirrhotic patients which they attribute to inclusion of a gamma globulin in the "fibrinogen" peak. In their second paper[108] they report marked elevations of a gamma globulin in cirrhotic sera, with smaller elevations in other liver diseases. The mobility of this fraction is said to be between the commonly described beta and gamma globulin fractions. Increases in this fraction were found to have little or no relationship to increased values obtained with protein flocculation reactions in the same sera.

Schmid[109] compared Kunkel's zinc turbidity procedure against gamma globulin values obtained by chemical salt fractionation in liver disease and obtained poor correlation.

Non-hepatic Diseases. As compared to hepatic disease this field has received but little attention from clinical investigators. However, strongly positive protein flocculation reactions are obtained in such diseases as malaria[110–112] and infectious mononucleosis[113,114] in a large percentage of cases. The formol-gel test has been found useful in kala-azar by Napier[115] and the Takata-Ara reaction was originally used in pneumonia.[30] The Weltmann reaction has been particularly employed in lung infections and is said to indicate "fibrotic or exudative" changes.[116] The cadmium sulfate test[34] has also been applied in this field. The colloidal gold test has been found by Carter and Maclagan[65] to give a high percentage of positive tests in such diseases as heart failure, malaria, infective endocarditis, glandular fever and rheumatoid arthritis. Fraser[117] has performed extensive studies of flocculation tests in rheumatoid arthritis and related diseases and reports that the colloidal gold reaction was positive in 61 per cent of the observations in rheumatoid arthritis and in 40 per cent of the cases of rheumatic fever.

Jacox and Gale[27] have found that the degree of turbidity produced by the reaction of serum with a quaternary ammonium salt (octab) reflects accurately the inflammatory activity in such diseases as rheumatic fever, chorea and rheumatoid arthritis.

Disturbances in protein metabolism, as measured by liver function tests, have been reported in rickettsial diseases such as Rocky Mountain spotted fever[118] and in bacterial diseases such as tuberculosis.[119] Electrophoretic studies of tuberculosis sera by Seibert and her co-workers[120] showed a rise in gamma globulin content in cases of minimal active tuberculosis. Such findings fit in rather well with an antigen-antibody mechanism for these diseases.[121]

CONCLUSION

Perhaps the best way to conclude this review is to quote the following paragraph from the excellent article on "Flocculation Tests: Chemi-

cal and Clinical Significance" by Maclagan[68] who has been one of the most productive workers in this field: "The possible application of the (flocculation) tests in protein chemistry and in immunology has been little explored. If they can detect differences between protein fractions which are *electrophoretically identical* they must have some contribution to the characterization of proteins in general." To which the author would like to add that, in his opinion, these developments can best be achieved by the application of *quantitative* physical and chemical measurements to the field of protein flocculation reactions.

Acknowledgment: I am grateful to Dr. Bruno W. Volk, Director of Laboratories of the Jewish Sanitarium and Hospital for Chronic Diseases for his encouragement and interest in the preparation of this review paper for publication. I am also grateful to Miss Renee Eisner for editing and typing the manuscript.

REFERENCES

1. Haurowitz, F. The Chemistry and Biology of Proteins, p. 155. New York, 1950. Academic Press.
2. Zeldis, L. J. and Madden, S. C. Clinical applications of biochemistry. Annual Review of Biochemistry, vol. 17, p. 340. Stanford, 1948. Annual Reviews, Inc.
3. Cantarow, A. and Trumper, M. Clinical Biochemistry, 4th ed., p. 97. Philadelphia, 1949. W. B. Saunders Co.
4. Hanger, F. M. Flocculation of cephalin-cholesterol emulsions by pathological serums. *Tr. A. Am. Physicians*, 53: 148, 1938.
5. Maclagan, N. F. Thymol turbidity test: a new indicator of liver dysfunction. *Nature*, 154: 670, 1944.
6. Neefe, J. R. Results of hepatic tests in chronic hepatitis without jaundice. Correlation with the clinical course and liver biopsy findings. *Gastroenterology*, 7: 1, 1946.
7. Kunkel, H. G. Estimation of alterations of serum gamma globulin by turbidimetric technique. *Proc. Soc. Exper. Biol. & Med.*, 66: 217, 1947.
8. Shank, R. E. and Hoagland, C. L. A modified method for the quantitative determination of thymol turbidity reaction of serum. *J. Biol. Chem.*, 162: 133, 1946.
9. Maclagan, N. F. Liver function tests in the diagnosis of jaundice. *Brit. M. J.*, 2: 197, 1947.
10. Lange, C. Die Ausflockung kolloidalen Goldes durch Zerebrospinalflüssigkeit bei luetischen Affektionen des Zentralnervensystems. *Ztschr. f. Chemotherap. Orig.*, 1: 44, 1912.
11. Gray, S. J. Studies of colloidal gold curve of blood serum in liver disease. *Proc. Soc. Exper. Biol. & Med.*, 41: 470, 1939.
12. Maclagan, N. F. The serum colloidal gold reaction as a liver function test. *Brit. J. Exper. Path.*, 25: 15, 1944.
13. Emanuel, G. Eine neue Reaktion zur Untersuchung des Liquor cerebrospinalis. *Berl. klin. Wchnschr.*, 52: 792, 1915.
14. Guillain, G., Laroche, G. and Lechelle, P. Étude comparative de la réaction du benzoin colloidal et de la réaction de la gomme mastic d'Emanuel. *Compt. rend. Soc. de Biol.*, 83: 1380, 1920.
15. Fischer, A. and Wiltner, W. Two new tests revealing hepatic damage. *Acta med. Scandinav.*, 134: 371, 1949.
16. Maizels, M. Empirical tests of liver function. *Lancet*, 2: 451, 1946.
17. Ducci, H. The colloidal red test for the study of hepatic dysfunction. *J. Lab. & Clin. Med.*, 32: 1273, 1947.
18. Saifer, A. Estimation of increased gamma globulin and fibrinogen in cerebrospinal fluid. A serial dilution-flocculation method. *J. Lab. & Clin. Med.*, 36: 130, 1950.
19. Wiseman, R. H. The nature of Henry's reaction in malaria. *Lancet*, 2: 543, 1934.
20. Dreyfuss, F. A dilution turbidity test in the serum in comparison with the thymol turbidity and cephalin-cholesterol flocculation tests. *J. Lab. & Clin. Med.*, 33: 672, 1948.
21. Love, E. B. and Mawson, C. A. Simplified flocculation tests for differential diagnosis of jaundice. *Lancet*, 1: 850, 1948.
22. Naumann, H. R. Saturation of serum with CO_2. A simple test for hyperglobulinemia. *Proc. Soc. Exper. Biol. & Med.*, 39: 378, 1938.
23. Gaté, J. and Papacostas, G. Une nouvella réaction des sérums syphilitiques: formolgélification. *Compt. rend. Soc. de biol.*, 83: 1432, 1920.
24. Wise, C. R. and Gutman, A. B. Formol-gel reaction: convenient preliminary test for hyperglobulinemia. *Am. J. M. Sc.*, 194: 263, 1937.
25. Gutman, A. B. The plasma proteins in disease. *Advances in Protein Chem.*, 4: 156, 1948.
26. Jacox, R. F. The reaction of human serum and component proteins of human plasma with a quaternary ammonium salt, Octab. *J. Lab. & Clin. Med.*, 37: 721, 1951.
27. Jacox, R. F. and Gale, R. G. The reaction of human serum with a quaternary ammonium salt. Results of a serial study in acute rheumatic fever. *J. Lab. & Clin. Med.*, 37: 728, 1951.
28. Mayer, R. L. and Eisman, P. C. Precipitation patterns of normal and pathologic blood sera with cationic detergents. *Proc. Soc. Exper. Biol. & Med.*, 77: 452, 1951.
29. Bronfin, G. J., Hart, R. W., Liebler, J. B. and Goldner, M. G. Precipitation of blood sera with a cationic detergent. A clinical evalution. *Proc. Soc. Exper. Biol. & Med.*, 77: 456, 1951.
30. Takata, M. and Ara, K. Uber eine neue kolloidchemische Liquorreaktion und ihre praktischen Ergebnisse. Tr. Sixth Congress Far Eastern A. Trop. Med., 1: 667, 1925.
31. Jezler, A. Die Takatasche Kolloidreaktion in Serum und Körperflussigkeiten und ihre Beziehungen zu Störungen des Eiweisstoffwechsels der Leber. *Ztschr. f. klin. Med.*, 114: 739, 1930.

32. MAGATH, T. B. The Takata-Ara test of liver function. *Am. J. Digest. Dis.*, 2: 713, 1935.
33. WAYBURN, E. and CHERRY, C. B. Takata reaction in blood serum. *Am. J. Digest. Dis.*, 5: 231, 1938.
34. WUNDERLY, C. and WUHRMANN, F. H. Die Cadmiumreaktion im Blutserum. *Schweiz. med. Wchnschr.*, 75: 1128, 1945.
35. WUNDERLY, C. and WUHRMANN, F. H. Effect of experimental increases in gamma globulin and albumin content of sera on response given by turbidity and flocculation tests. *Brit. J. Exper. Path.*, 28: 286, 1947.
36. GROS, W. Eine neue, einfache Flockungsreaktion mit Hayemscher Lösung. *Klin. Wchnschr.*, 18: 781, 1939.
37. MANDEL, E. E., PARIS, D. A. and HARRIS, D. T. Evaluation of the flocculation test with Hayem's solution. *J. Lab. & Clin. Med.*, 34: 653, 1949.
38. GORTNER, R. A. and GORTNER, W. A. Outlines of Biochemistry, p. 206. New York, 1949. John Wiley & Sons.
39. HARDY, W. D. Eine vorläufige Untersuchung der Bedingungen welche die Stabitität von nicht umkehrbaren Hydrosolen bestimmen. *Z. physik. Chem.*, 33: 385, 1900.
40. ELLIS, R. Die Eigenschaften der Ölemulsionen. I. Die elektrische Ladung. *Z. physik. Chem.*, 78: 321, 1912.
41. POWIS, F. The coagulation of colloidal arsenious sulphide by electrolytes and its relation to the potential difference at the surface of the particles. *J. Chem. Soc.*, 109: 734, 1916.
42. HELMHOLTZ, H. VON. I. Studien über electrische Grenzschichten. *Ann. d. Phys. u. Chem., Leipz.*, 7: 337, 1879.
43. GOUY, G. Constitution of the electric charge at the surface of an electrolyte. *J. Physique*, 9: 457, 1910.
44. FREUNDLICH, H. Kapillarchemie, vol. I, 4th ed., p. 356. Leipzig, 1930. Akademische Verlagsgesellschaft.
45. HAUSER, E. A. Modern colloidchemical concepts of the phenomenon of coagulation. *J. Phys. & Colloid Chem.*, 55: 605, 1951.
46. SAIFER, A. Studies with the quantitative cephalin-cholesterol flocculation reaction. 1. Effect of temperature variation. Serum protein patterns in liver disease. *Am. J. M. Sc.*, 219: 597, 1950.
47. SAIFER, A. A method for the quantitative determination of the cephalin-cholesterol flocculation reaction. *J. Clin. Investigation*, 27: 737, 1948.
48. EILERS, H. and KORFF, J. Significance of the phenomenon of the electrical charge on the stability of hydrophobic dispersions. *Tr. Faraday Soc.*, 36: 229, 1940.
49. COHN, E. J. et al. A system for the separation of the components of human blood: quantitative procedures for the separation of the protein components of human plasma. *J. Am. Chem. Soc.*, 72: 465, 1950.
50. MICHAELIS, L. The Effects of Ions in Colloidal Systems. Baltimore, 1925. Williams & Wilkins Co.
51. BAUER, R. Zur Klinik und Serologia der Myelomkrankheit. *Med. Klin.*, 31: 679, 1935.
52. KUNKEL, H. G., AHRENS, E. H., JR. and EISENMENGER, W. J. Application of turbidimetric methods for estimation of gamma globulin and total lipid of patients with liver disease. *Gastroenterology*, 11: 499, 1948.
53. GRAY, S. J. Colloidal gold reaction of blood serum in diseases of the liver. *Arch. Int. Med.*, 65: 523, 1940.
54. GRAY, S. J. Studies on mechanism of spinal fluid colloidal gold reaction. *Proc. Soc. Exper. Biol. & Med.*, 51: 401, 1942.
55. KABAT, E. A., MOORE, D. H. and LANDOW, H. Electrophoretic study of protein components in cerebrospinal fluid and their relationship to serum proteins. *J. Clin. Investigation*, 21: 571, 1942.
56. MACLAGAN, N. F. and BUNN, D. Flocculation tests with electrophoretically separated serum proteins. (Abstr.) *Biochem. J.*, 41: 19, 1947.
57. KABAT, E. A., HANGER, F. M., MOORE, D. H. and LANDOW, H. Relation of cephalin flocculation and colloidal gold reactions to serum proteins. *J. Clin. Investigation*, 22; 563, 1943.
58. MOORE, D. B., PIERSON, P. S., HANGER, F. M. and MOORE, D. H. Mechanism of the positive cephalin-cholesterol flocculation reaction in hepatitis. *J. Clin. Investigation*, 24: 296, 1945.
59. HANGER, F. M. Abnormalities in the globulin component of serum as demonstrable by the cephalin flocculation test. *Tr. A. Am. Physicians*, 60: 82, 1947.
60. MACLAGAN, N. F. and BUNN, D. Flocculation tests with electrophoretically separated serum proteins. *Biochem. J.*, 41: 580, 1947.
61. WATSON, C. J. and RAPPAPORT, E. M. A comparison of the results obtained with the Hanger cephalin-cholesterol flocculation test and the Maclagan thymol turbidity test in patients with liver disease. *J. Lab. & Clin. Med.*, 30: 983, 1945.
62. RECANT, L., CHARGAFF, E. and HANGER, F. M. Comparison of the cephalin-cholesterol flocculation with the thymol turbidity test. *Proc. Soc. Exper. Biol. & Med.*, 60: 245, 1945.
63. MACLAGAN, N. F. The thymol turbidity test as an indicator of liver dysfunction. *Brit. J. Exper. Path.*, 25: 234, 1944.
64. COHEN, P. P. and THOMPSON, F. L. Mechanism of the thymol turbidity test. *J. Lab. & Clin. Med.*, 32: 475, 1947.
65. CARTER, A. B. and MACLAGAN, N. F. Some observations on liver function tests in diseases not primarily hepatic. *Brit. M. J.*, 2: 80, 1946.
66. KUNKEL, H. G. and HOAGLAND, C. L. Mechanism and significance of the thymol turbidity test for liver disease. *J. Clin. Investigation*, 26: 1060, 1947.
67. WUHRMANN, F. H. and WUNDERLY, C. The cadmium reaction. *J. Lab. & Clin. Med.*, 34: 1162, 1949.
68. MACLAGAN, N. F. Flocculation tests: chemical and clinical significance. *Brit. M. J.*, 2: 892, 1948.
69. DUCCI, H. The thymol test of Maclagan: standardization and adaptation to the Evelyn photoelectric colorimeter. *J. Lab. & Clin. Med.*, 32: 1267, 1947.
70. MACFARLAND, H. N. and HARWOOD, J. H. Transactions, Conference on Liver Injury, pp. 73–75. Fifth meeting. New York, 1946. Josiah Macy, Jr. Foundation.

71. Neefe, J. R. and Reinhold, J. G. Photosensitivity as a cause of falsely positive cephalin-cholesterol flocculation tests. *Science*, 100: 83, 1944.
72. Steinberg, A. Cholesterol-desoxycholic acid: a stable antigen for use in a flocculation test for liver dysfunction. I. Comparison with the Hanger cephalin-cholesterol flocculation test. *J. Lab. & Clin. Med.*, 34: 1049, 1949.
73. Bruger, M. Fractional cephalin-cholesterol flocculation in hepatic disease. *Science*, 97: 585, 1943.
74. Mirsky, I. M. and Von Brecht, R. The fractional cephalin-cholesterol flocculation test. *Science*, 98: 499, 1943.
75. Makari, J. G. A non-specific resistance factor in the albumin residue revealed by the serial cephalin flocculation test. *Nature*, 160: 201, 1947.
76. Makari, J. G. Cephalin-cholesterol flocculation test in kala azar. *J. Trop. Med.*, 49: 113, 1946.
77. Makari, J. G. Serial cephalin flocculation curves: their application in the study of tropical diseases and their relation to a new resistance factor. *J. Trop. Med.*, 51: 8, 1948.
78. Frisch, A. W. and Quilligan, J. J., Jr. Modified cephalin-cholesterol test in study of hepatic disease. *Am. J. M. Sc.*, 212: 143, 1946.
79. Lepehne, G. M. Studies on ascitic fluid in patients with hepatic cirrhosis, heart failure and cancer. Results of cephalin-cholesterol flocculation, thymol turbidity, methylene blue, qualitative and quantitative bilirubin and other tests. *Am. J. Digest. Dis.*, 18: 86, 1951.
80. Dauphinee, J. A. and Campbell, W. R. Serum proteins in hepatic disease. *M. Clin. North America*, 32: 455, 1948.
81. Wolfson, W. Q., Cohn, C., Calvary, E. and Ichiba, F. Studies in serum proteins. Rapid procedure for estimation of total proteins, true albumins, total globulin, alpha globulin, beta globulin and gamma globulin. *Am. J. Clin. Path.*, 18: 723, 1948.
82. Huerga, J. de la and Popper, H. Estimation of serum gamma globulin concentration by turbidimetry. *J. Lab. & Clin. Med.*, 35: 459, 1950.
83. Huerga, J. de la, Popper, H., Franklin, M. and Routh, J. I. Comparison of the results of gamma globulin and zinc sulfate turbidity test with electrophoretic determination of the gamma globulins. *J. Lab. & Clin. Med.*, 35: 466, 1950.
84. Ricketts, W. E., Sterling, K. and Levine, R. S. Gamma globulin determinations. Comparative values obtained by turbidimetric and electrophoretic methods. *J. Lab. & Clin. Med.*, 38: 153, 1951.
85. Saifer, A. and Zymaris, M. C. Photometric microdetermination of human gamma globulin. I. Development of a quantitative flocculation-ninhydrin procedure. *J. Clin. Investigation*, 31: 1–11, 1952.
86. Moore, S. M. and Stein, W. H. Photometric ninhydrin method for use in the chromatography of amino acids. *J. Biol. Chem.*, 176: 367, 1948.
87. Saifer, A., Zymaris, M. C. and Berger, H. Photometric microdetermination of human gamma globulin. II. Comparison of quantitative flocculation-ninhydrin method with electrophoretic method. *J. Clin. Investigation*, 31: 12–22, 1952.
88. Kafka, V. Die Zerebrospinalflüssigkeit. Leipzig and Vienna, 1930. F. Deuticke.
89. Kabat, E. A., Landow, H. and Moore, D. H. Electrophoretic patterns of concentrated cerebrospinal fluid. *Proc. Soc. Exper. Biol. & Med.*, 49: 260, 1942.
90. Delcourt, R. and Manet, C. Application au liquide céphalo-rachidien des réactions de floculation sérique. Le thymol-test. *Acta neurol. et psychiat. belg.*, 49: 96, 1949.
91. Donovan, A. M., Foley, J. M. and Moloney, W. C. The precipitation of cerebrospinal fluid globulin by zinc sulfate. *J. Lab. & Clin. Med.*, 37: 374, 1951.
92. Schrumpf, C. A. A. Present fundamentals of some liver function tests. *Am. J. Digest. Dis.*, 15: 367, 1948.
93. Steigmann, F., Popper, H., Hernandez, R. and Shulman, B. Flocculation tests in the diagnosis of hepato-biliary disease. *Gastroenterology*, 13: 9, 1949.
94. Linder, H. K., Bruger, M. and Greene, C. H. Comparative studies with some newer tests for hepatic dysfunction. *New York State J. Med.*, 48: 1371, 1948.
95. Klatskin, G. Some observations on liver function tests. *Yale J. Biol. & Med.*, 21: 128, 1948.
96. Gutman, A. B. and Hanger, F. M. Differential diagnosis of jaundice by combined serum phosphatase determination and cephalin flocculation. *M. Clin. North America*, 25: 837, 1941.
97. Popper, H. and Steigmann, F. Differential diagnosis between medical and surgical jaundice by laboratory tests. *Ann. Int. Med.*, 29: 469, 1948.
98. Mawson, C. A. Single-sample tests in the differential diagnosis of jaundice. *J. Clin. Path.*, 1: 167, 1948.
99. Kibrick, A. C. and Clements, A. B. A comparative study of the serum albumin-globulin ratio, the cephalin-cholesterol flocculation, and the thymol turbidity tests for liver function. *J. Lab. & Clin. Med.*, 33: 662, 1948.
100. Ernst, R. G. and Dotti, L. B. An evaluation of the thymol turbidity test. *Am. J. M. Sc.*, 216: 316, 1948.
101. Strade, H. A., Dotti, L. B. and Ilka, S. J. A clinical evaluation of a new liver function test, the colloidal red test, in comparison with the thymol turbidity test. *Am. J. M. Sc.*, 217: 448, 1949.
102. Oppenheim, E., Bruger, M. and Frost, E. The colloidal red test as an index of liver dysfunction. *J. Lab. & Clin. Med.*, 34: 662, 1949.
103. Franklin, M., Popper, H., Steigmann, F. and Kozoll, D. D. Relation between structural and functional alterations of the liver. *J. Lab. & Clin. Med.*, 33: 435, 1948.
104. Mateer, J. G. et al. Combined liver biopsy and liver function study in 132 cases of cholelithiasis and 31 cases of peptic ulcer (operated cases). Emphasis upon early microscopic liver disease and particularly acute infiltrative hepatitis and

microscopic periportal cirrhosis. *Gastroenterology*, 11: 284, 1948.

105. Ricketts, W. E., Kirsner, J. B., Palmer, W. L. and Sterling, K. Observations on the diagnostic value of liver biopsy test, of hepatic function and electrophoretic fractionation of serum proteins in asymptomatic portal cirrhosis. *J. Lab. & Clin. Med.*, 35: 403, 1950.
106. Rafsky, H. A. et al. Electrophoretic studies in liver disease. *Gastroenterology*, 14: 29, 1950.
107. Franklin, M. et al. Electrophoretic studies in liver disease. I. Comparison of serum and plasma electrophoretic patterns in liver disease with special reference to fibrinogen and gamma globulin patterns. *J. Clin. Investigation*, 30: 718, 1951.
108. Franklin, M. et al. Electrophoretic studies in liver disease. II. Gamma$_1$ globulin in chronic liver disease. *J. Clin. Investigation*, 30: 729, 1951.
109. Schmid, R. The zinc turbidity test and its clinical application. *J. Lab. & Clin. Med.*, 36: 52, 1950.
110. Guttman, S. A. et al. Significance of cephalin-cholesterol flocculation test in malarial fever. *J. Clin. Investigation*, 24: 296, 1945.
111. Lippincott, S. W., Ellerbrook, L. D., Hesselbrock, W. B., Gordon, H. H., Gottleib, L. and Marble, A. Liver function tests in chronic relapsing vivax malaria. *J. Clin. Investigation*, 24: 616, 1945.
112. Keys, A., Wells, S., Hoffbauer, F. W., Taylor, H. L. and Henschel, A. Experimental malaria in man. II. Liver function. *J. Clin. Investigation*, 29: 52, 1950.
113. De March, Q. B. and Alt, H. L. Hepatitis without jaundice in infectious mononucleosis. *Arch. Int. Med.*, 80: 257, 1947.
114. Evans, A. S. Liver involvement in infectious mononucleosis. *J. Clin. Investigation*, 27: 106, 1948.
115. Napier, L. E. A new serum test for kala-azar. *Indian J. M. Research*, 9: 830, 1922.
116. Gradwohl, R. B. H. Clinical Laboratory Methods and Diagnosis, 3rd ed. London, 1943. Henry Kimpton.
117. Fraser, T. N. Flocculation tests in rheumatoid arthritis. *Ann. Rheumat. Dis.*, 7: 83, 1948.
118. Wolff, W. A. and Harrell, G. T. Liver and kidney function in Rocky Mountain spotted fever. *Am. J. M. Sc.*, 218: 500, 1949.
119. Levinson, S. A. and Klein, R. I. Weltmann serum coagulation reaction: comparison with sedimentation reaction and with clinical findings in pulmonary tuberculosis. *Am. Rev. Tuberc.*, 37: 200, 1938.
120. Seibert, F. B., Seibert, M. V., Atno, A. J. and Campbell, H. W. Variation in protein and polysaccharide content of sera in chronic diseases, tuberculosis, sarcoidosis and carcinoma. *J. Clin. Investigation*, 26: 90, 1947.
121. Brown, T. McP., Wichelhausen, R. H., Merchant, W. R. and Robinson, L. B. A study of the antigen-antibody mechanism in rheumatic diseases. *Am. J. M. Sc.*, 221: 618, 1951.

Current Principles of Management in Gout*

ALEXANDER B. GUTMAN, M.D. *and* T. F. YÜ, M.D.
New York, New York

No cure for gout is now available or in prospect. Nevertheless, substantial advances in the regulation of gout have been made in recent years and the consequences of the disorder can be minimized and counteracted more effectively than hitherto.

For example, in the treatment of acute gouty arthritis it is now possible to abort and terminate acute attacks more quickly and regularly, and with fewer residual discomforts. In the prevention of acute seizures one can, by fairly dependable prophylaxis, so reduce the frequency and severity of acute gouty attacks that even severely afflicted patients, with few refractory exceptions, suffer relatively infrequent interruption of normal activities. In chronic gouty arthritis, a neglected phase of the gout problem, it is no longer necessary passively to await the development of deforming or crippling tophaceous deposits, which are then treated palliatively by surgical drainage or, more drastically, by amputation. It now seems feasible, by combined dietary restriction and regular use of suitable uricosuric drugs, to obviate the formation of tophaceous deposits, to prevent the further enlargement of tophi already formed, and even to mobilize long-established tophi in some instances.

These advances in management have come about for the most part as the result of systematic empirical exploitation of the potentialities of old drugs, such as colchicine, and the development of new therapeutic agents. In part, however, they are the fruit of investigations giving better insight into the fundamental nature of the gouty trait and the causes of acute gouty arthritis and chronic tophaceous gout. Even though the basic problems of gout still are largely unsolved, a brief review of these newer concepts of the pathogenesis of the disorder will serve well to introduce the philosophical considerations underlying current principles of management.

FUNDAMENTAL NATURE OF THE GOUTY TRAIT

According to available evidence, gout as a primary disease (i.e., not secondary to polycythemia vera, etc.) is due to a genetically determined inborn error of purine metabolism. Analysis of gouty families reveals inheritance of the fault as a single dominant trait with incomplete penetrance, particularly incomplete, for obscure reasons, in female carriers.[1–3] The transmitting gene is autosomal, not sex-linked.

There is some indication of the general nature of the underlying metabolic anomaly in gout. In some instances overproduction of urate can be demonstrated. Thus, contrary to earlier views based upon sparse data obtained largely by inadequate methods, the urinary excretion of urate in gouty subjects on a fixed, low purine diet significantly exceeds the normal maximum in an appreciable proportion of cases, about 25 per cent of 100 gouty subjects studied in a recent survey.[4] Moreover, when such gouty subjects excreting excessive amounts of urate in the urine are fed N^{15}-labeled glycine, a precursor of uric acid in biosynthesis, unequivocally greater than normal quantities of N^{15} are found in the excreted urate.[5] This finding is taken to indicate that in such gouty subjects there is some diversion of precursor nitrogen and carbon compounds from metabolic pathways ordinarily terminating in urea formation, among others, to those ending in urate. The rapidity with which N^{15} is incorporated into urate under these circumstances would seem to exclude intermediary incorporation into nucleic acids, which have a slow turnover rate. A more direct pathway of urate biosynthesis from simple carbon and nitrogen precursors appears to be present and abnormally active in such cases of gout. The nature of this pathway is not known but direct purine biosynthesis from glycine, "formate," ammonia, bicarbonate and ribose-1-

* From the First Medical Service, The Mount Sinai Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York City. Supported in part by a grant-in-aid from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and from the John A. Hartford Foundation.

phosphate, with intermediary formation of 4-amino-5-imidazole carboxamide ribotide, has been convincingly demonstrated in the pigeon and rat.[6–8]

The metabolic anomaly in gout is more complex than this, however. In gouty subjects not excreting excessive amounts of urate, feeding experiments with N^{15}-labeled glycine have failed to show excessive incorporation of N^{15} into excreted urate.[9] Whether this means that urate biosynthesis is not augmented in these cases, or so slightly or intermittently as not to be detectable by this method, cannot now be ascertained. Moreover, it is altogether probable that increased degradation of nucleic acids, whether from endogenous or exogenous sources, is a contributory factor in some cases of gout. At present the evidence that uricolysis plays a significant role in gout is unsubstantial.

The capacity to excrete urate and other purines doubtless is as important a factor in the pathogenesis of gout, certainly of chronic tophaceous gout, as is the rate of elaboration of these substances. In this aspect of regulation of the purine economy the kidney plays a predominant role. No primary, intrinsic defect in renal excretion of urate has yet been detected in gouty subjects, even with the most refined available methods for assessing discrete renal functions.[10–12] There is in the gouty subject,[10,11,13] as in normal man,[14,15] complete filtration of urate at the glomerulus, with subsequent tubular reabsorption, by enzymatic transfer systems as yet unidentified, of all but 5 to 10 per cent of the filtered urate. Despite the high incidence of renal damage in chronic gout, these normal processes appear to be substantially maintained even when, as often occurs, the glomerular filtration rate and effective renal plasma flow are markedly reduced.[10,13] The tenacity with which efficient tubular reabsorption of urate is preserved, even in advanced tophaceous gout, deserves special comment. It is difficult to comprehend the purposefulness of almost complete tubular reabsorption of uric acid, an apparently useless end product of purine metabolism, in normal man. Persistent maintenance of this activity in the face of chronic tophaceous gout would seem, in fact, to be distinctly deleterious.

CAUSES OF ACUTE GOUTY ARTHRITIS

It has been suggested[16,17] that the diverse precipitating causes of acute gout—local trauma, dietary and alcoholic overindulgence, infections, surgical operations, emotional upsets, etc. —are, in effect, non-specific stresses which elicit an alarm reaction taking the form, in the individual predisposed to gout, of acute gouty arthritis. There is, however, no convincing evidence that gout is primarily an endocrine disease of the pituitary or adrenal glands[18,19] nor has the role of the gonads, which seem in part to predetermine the incidence of manifest gouty symptoms, been satisfactorily clarified.[20] In regard to acute gouty arthritis as an allergic phenomenon, all that can be said at present is that allergic reactions may incite an acute gouty attack[21] but probably do so only in a minority of allergic individuals also inherently predisposed to gout.

The immediate agency of acute gouty arthritis is not known. Despite common acceptance of the assumption that precipitation of uric acid in affected joints somehow evokes the acute attack, there is no valid evidence that uric acid *per se*, pharmacologically a virtually inert substance, is the offending agent; and there is a great deal of circumstantial evidence that it is not.[22] One may conjecture that the real culprit is a purine precursor of uric acid with potent vasomotor properties, of which a number are known. If so, this substance has not been identified; nor is it known whether the responsible agent is an abnormal metabolite formed only in gout or a normal metabolite formed in excess or improperly degraded or excreted.

CAUSES OF CHRONIC TOPHACEOUS GOUT

Here we are on firmer ground. While uric acid is a physiologically innocuous substance, its relative insolubility in blood plasma predisposes to precipitation in the tissues as plasma levels rise, particularly if there is significant impairment of renal excretion of urate; why urate should be deposited by predilection in cartilage is not clear. These urate deposits in the tissues are, at first, painless and probably harmless but with increase in size they impinge upon neighboring structures and, acting as foreign body irritants, may elicit chronic inflammatory reactions and acute secondary infections. In the joints very large deposits lead ultimately to deforming and incapacitating arthritis; in the kidneys sometimes to formation of kidney stones, obstruction of the collecting tubules and uremia.

The development of tophaceous deposits is an indication of positive urate balance, i.e., the rate

of excretion (and degradation) of urate is inadequate to cope with the rate of urate production. This may be the result solely of excessive biosynthesis of urate from simple carbon and nitrogen precursors and the degradation products of ingested purines, abetted by large dietary intake of proteins and preformed purines; or only of impairment of renal excretion of urate and other purines; but in most instances of chronic tophaceous gout both factors appear to operate together.

Even if urate retention is of minor degree and intermittent, it is apt to be cumulative over the years. Visible tophi develop in some 50 per cent of patients with chronic gout,[23] a minimum approximation of the incidence of tissue urate deposits since it takes into account only superficial accumulations. Estimations of the miscible pool of urate[24] and of the total mobilizable body urate[25] indicate that insidious deposition of urate in the tissues is, in fact, a more or less regular accompaniment of chronic gout. Fortunately, these depositions progress to gross deformity and crippling arthritis only in the minority of cases.

GENERAL PRINCIPLES OF MANAGEMENT

It is apparent from the preceding discussion that correction of the ultimate causes of gout, involving obscure enzyme reactions in unidentified tissues, is not now possible.

It is also apparent that proper regulation encompasses not one but two more or less distinct objectives. The first is *suppression of the acute attacks* which, as already indicated, are not ascribable to uric acid *per se* but to as yet unidentified agents. The traditional drug employed for this purpose is colchicine, a specific of unknown pharmacologic action which has no detectable effect on uric acid metabolism and, while effective in the control of acute gouty arthritis, does not prevent the insidious development of chronic tophaceous gout. It is futile to judge the efficacy of any measures taken to prevent or control acute attacks by changes in serum or urine uric acid content, or by any other laboratory test now available. Until the true causative agent is identified and can be measured, this must be done by clinical trial and error over prolonged periods of close observation. The unpredictable vagaries of acute gouty arthritis preclude early judgment.

In the more severe and progressive cases of chronic gout, particularly with the development of renal damage, there is added to the necessity for prophylaxis and control of acute seizures a second need, that of *prevention and mobilization of urate deposits in the tissues*. To achieve this a state of negative urate balance must be induced for as long as may be required. This is best accomplished by limiting the formation of urate in the body, insofar as this is possible, by restriction of the dietary intake of precursor purines, proteins and fat and, at the same time, accelerating the excretion of urate by regular and protracted use of a suitable uricosuric agent to counteract persistent tubular reabsorption of urate. The resultant fall in serum urate levels, particularly if marked, presumably helps to reverse the equilibrium favoring flow of urate from the blood into the tissues. The adequacy of such measures is best judged by periodic measurement of the urinary and serum uric acid content on a fixed diet. Eventually, the results of treatment may become evident clinically in the failure of new tophi to appear; in greater mobility of affected joints particularly of the feet and knees; and in reduction in size of established tophi, as shown objectively by comparison with pre-treatment photographs and x-rays. There is no clear indication as yet that uricosuric agents, at least by virtue of their uricosuric effect, are of definite benefit in controlling or preventing acute gouty attacks.

Finally, it is apparent that the prophylactic and therapeutic objectives to be sought in gout depend, in general, upon the stage of development of the disease: whether the patient is in (1) the initial phase of *asymptomatic "essential" hyperuricemia*, (2) the critical phase of *acute gouty arthritis*, (3) the more or less quiescent interval phase between acute attacks, *intercritical gout* or (4) the ultimate phase of *chronic tophaceous gout*, with more or less chronic joint disability punctuated by recurrent acute arthritis, and usually associated with more or less renal damage.

Asymptomatic "essential" hyperuricemia has been disclosed by systematic study of the families of patients with overt gout to be more common than is generally appreciated.[1–3] Most bearers of the gouty trait apparently reveal the metabolic fault only as hyperuricemia, if at all, and never develop recognizable clinical symptoms of gout; this is particularly true of female carriers. In view of this generally benign course it would seem unwise to impose severe dietary restrictions or prescribe regular prophylactic

therapy in this phase of the disease. As a prudent precaution, however, reasonable limitation of the diet, including alcoholic intake, should be advised.

With the first overt attack of acute gouty arthritis, the prospect of progression of the disorder is greatly enhanced since recurrence is the rule. Whether these recurrences will be so infrequent as to cause no more than very occasional, if painful, interruption of activities or so frequent as virtually to incapacitate the patient cannot be prognosticated at the time of the first attack; however, onset of the initial attack before the age of thirty-five, marked familial incidence of overt gout, and a fulminating initial seizure involving several joints all seem to predispose to a more severe outcome. In any event, the acute attack is treated as early and vigorously as possible with colchicine, ACTH or phenylbutazone, singly or in combination.

With subsidence of the seizure, it is necessary to face the problem of prophylaxis during the intercritical period. This probably is not necessary until it becomes evident that recurrences will be frequent and severe. It is best accomplished, at present, by instituting regular colchicine prophylaxis and more or less restriction of diet, depending upon individual idiosyncrasies.

In chronic gout, in addition to regular prophylaxis to prevent acute recurrences, it is good practice to institute a more rigidly restrictive diet in order not to overburden the patient with excessive and unnecessary urate loads. Usually this diet subsequently can be liberalized somewhat, particularly if uricosuric agents are employed, depending upon the effect on serum and urinary urate levels, and upon the patients' personal tolerances. A suitable uricosuric agent, usually benemid,® is given concomitantly in appropriate dosage if there is indication of significant urate deposition in the tissues.

So much, in bare outline, for the general objectives and principles of management. Let us now examine in greater detail the several agents presently available to accomplish these objectives, indicating their advantages and limitations.

COLCHICINE

There are three more or less distinct uses for colchicine in the management of gout: (1) to terminate established attacks of acute gouty arthritis, the classic usage; (2) to abort impending attacks of acute gout and (3) as a prophylactic agent to prevent recurrence of acute seizures in the intercritical periods of chronic gout. As already indicated, colchicine is not a uricosuric agent.

To terminate established attacks of acute gouty arthritis, colchicine traditionally is given orally in divided doses of 0.5 or 1.0 mg. every two to four hours until the attack subsides or diarrhea, nausea or vomiting ensue. Usually, substantial relief of local and systemic manifestations is obtained after a total dosage of 6 to 8 mg. Colchicine, however, is by no means promptly and completely effective in all cases of acute gout, particularly if treatment has been delayed for days or weeks. There is a significant incidence of refractory response. In at least 25 per cent of the eighty-seven attacks in forty-six gouty subjects we have treated in this way there was persistence of swelling and pain of greater or lesser degree, sometimes for weeks. Moreover, the gastrointestinal effects of colchicine not infrequently are unduly prolonged, debilitating and difficult to control even with paregoric; if peptic ulcer, spastic colon or similar disorders are present these side effects may be extremely troublesome. Despite the entrenched position of colchicine in the treatment of acute gouty arthritis, there is ample opportunity for alternative or supplementary therapy.

Little has appeared in the literature concerning the intravenous use of colchicine for acute gouty arthritis but this mode of administration has been widely employed for many years. Enthusiastic proponents of intravenous colchicine therapy claim for it prompt and striking relief of symptoms with a minimum of gastrointestinal discomfort. Our own experience with intravenous colchicine is very limited. Of fourteen acute gouty attacks so treated, in four there was dramatic relief after one injection (0.65 mg. colchicine); in eight the response was favorable but incomplete; in two no relief was obtained even after several injections. There were no gastrointestinal complications after a single injection but these appeared when multiple doses were given. This form of colchicine therapy appears to have a place in the treatment of acute gouty arthritis but more systematic evaluation is needed.

The second use of colchicine is to abort impending attacks of acute gout, the onset of which is often heralded by twinges of pain,

tenderness or stiffness in a joint, or other indisposition recognized by the observant patient. For this purpose the patient is instructed to take 0.5 or 1.0 mg. every two hours upon the first intimation of an attack, until a total of 3 or 4 mg. has been ingested. This dosage does not ordinarily produce gastrointestinal symptoms but will usually prove effective if taken in time. Control of acute gouty arthritis, irrespective of the agency employed, is almost always more satisfactory if instituted early.

The third important use of colchicine, the regular administration of small doses for prevention of recurrence of acute attacks, seems to be a comparatively recent innovation in colchicine therapy. Cohen in 1936 advised ingestion of 0.5 mg. three times daily for one week in every four during the symptom-free intervals, in conjunction with continued low purine diet, and claimed good results.[26] Talbott[10] recommends one or two colchicine tablets every week throughout the year for those who have but few attacks, increased to a regular ration of one to three tablets daily in those subject to very frequent recurrence. He states that the practice is "believed to be beneficial."[10] Our own custom is to employ regular colchicine prophylaxis, in conjunction with dietary restriction, whenever justified by frequent recurrence of acute attacks. The minimum effective dosage is determined by patient trial and error, according to individual needs. Usually 1.0 or 0.5 mg. every night or every other night will suffice; in the more refractory cases 1.5 or 2.0 mg. nightly may be required. These dosages cause no gastrointestinal discomfort in most patients, drug tolerance does not develop and bone marrow or liver toxicity thus far has not been detected.

Of seventy-three of our gouty patients now on this prophylactic regimen, in forty-seven appraisal of the results must be withheld for the present because the incidence of prior attacks was too erratic and the period of prophylaxis is still too short. Observations on the effects of regular colchicine prophylaxis over a period of eighteen months to four years or more are available in thirty-one cases. (Table I.) In eighteen the results have been conspicuously good, with reduction of regularly recurrent severe or moderately severe attacks to few, if any, minor episodes; in thirteen instances the response has, in fact, made the difference between virtual incapacitation because of frequent interruption of activities and restoration to full employment. In eight patients the results of prophylaxis have been incomplete or equivocal. In five instances there has been no significant acute arthritis throughout the period of prophylaxis but the infrequency of prior seizures makes judgment difficult as yet.

Colchicine prophylaxis is, at best, a compromise form of suppressive therapy and there are no adequate data as to its efficacy available in the literature. The experience summarized in Table I is inadequate for final evaluation but the results to date are the most satisfactory we have obtained by any prophylactic regimen tried. The effective preventative properties of cinchophen, as recorded in detail by Bartels[27] in 1943, are, unfortunately, vitiated by occasional hepatotoxicity and this form of prophylaxis has now been virtually abandoned in this country.

CORTICOTROPIN (ACTH)

The chief use for ACTH in gout is to terminate established attacks of acute arthritis, for which purpose it is a potent agent in most instances if given in adequate amounts according to a proper dosage schedule. It is effective in most cases responding unsatisfactorily to colchicine and has the advantage of not causing gastrointestinal upset. Its action is unspecific and appears to be suppressive and antiphlogistic through unknown mechanisms. Compound F also appears to be effective[28] whereas oral cortisone, although it may be adequate in sufficient dosage, is not dependable. ACTH increases the urinary excretion of urate but causes too many side reactions to justify protracted regular use as a prophylactic and uricosuric agent in chronic gout.

We have thus far treated forty acute gouty attacks by intramuscular injection of ACTH in aqueous medium. (Table II.) Whereas our earlier experience indicated inadequate response in some 30 per cent of cases treated with a maximum daily dose of 100 mg.,[18] this proportion has declined to 10 per cent with the realization that larger doses may be required in the first days of treatment, as was necessary in eight of our cases. In another 10 per cent of cases the response was less complete and more protracted. Our present practice is to initiate ACTH therapy in acute gouty arthritis with one to four injections of 50 mg. on the first day of treatment (total 50 to 200 mg., usually 100 mg. per day). Daily doses of 50 to 200 mg. are maintained for

TABLE I

RESULTS OF REGULAR COLCHICINE PROPHYLAXIS OVER A PERIOD OF EIGHTEEN MONTHS OR MORE IN THIRTY-ONE CASES OF CHRONIC GOUT

Case		Tophi	Years of Prophylaxis	Daily Colchicine (mg.)	Course before and during Prophylactic Regimen*				Remarks
No.	Name and Age				Years	Attacks/Year			
						Severe	Moderate	Mild	
1	I. G., 76	0	7	0.5	1939–44	1	1	0	Did well on prophylactic regimen; both attacks after 1944 were due to omission of colchicine
					1944–48	0	0	0	
					1948–49	0	0	2	
					1949–51	0	0	0	
2	R. C., 48	++	6	1	1931–42	0	1	2	Prior to prophylaxis, incapacitated 8–10 wk/yr. and unable to hold regular job; since prophylaxis he has been working almost without interruption
					1942–46	4–5	0	0	
					1946–48	0	0	0	
					1948–52	1	0	1	
3	C. M., 64	0	5	1	1933–44	0	1–4	0	No joint complaints for last three years; died 1949, probably coronary thrombosis
					1944–47	0	0	2–3	
					1947–49	0	0	0	
4	M. M., 54	+	4	0.5	1927–45	1	1	0	Constant joint pain without free intervals for some months before prophylaxis; these minor attacks abated for 2 yr. after the regimen was begun but there has been some recurrence
					1945–48	2	1	0	
					1948–50	0	0	0	
					1950–52	0	2	1	
5	G. W., 46	0	4	1.5–2.0	1940–48	1	0	0	Control of acute attacks by prophylaxis incomplete; benefit problematic
					1948–51	1	1	0	
					1951–52	1	0	2	
6	E. S., 45	0	4	0.5–1.0	1937–48	1	1	2	Free of complaints when following regimen; invariable acute attack when colchicine omitted
					1948–50	0	0	3	
					1950–52	0	0	2	
7	P. M., 73	0	4	0.5 q. 2.d.	1945–48	0	1	1	Number of acute attacks prior to prophylaxis were too few for evaluation of prophylactic regimen
					1948–49	0	1	0	
					1949–51	0	0	0	
					1951–52	0	1	0	
8	L. R., 70	++	3½	1	1933–44	1	2	0	Working regularly since prophylactic regimen started
					1944–49	3	4	0	
					1949–51	0	1	0	
					1951–52	0	0	2	
9	D. R., 36	0	3½	1	1944–45	0	3–4	0	Number of acute attacks per year decreased; some of the attacks on the regimen attributable to omission of colchicine
					1945–49	6–7	0	0	
					1949–50	2	1	0	
					1950–52	1	1	1	
10	O. G., 49	0	3½	0.5	1947–49	0	1	1	One acute attack developed after omission of colchicine
					1949–51	0	0	0	
					1951–52	0	0	1	
11	E. F., 50	++++	3	1	1942–49	2	2	Many	Chronic diffuse joint pain disappeared with colchicine prophylaxis; persistent mild attacks
					1949–52	0	0	4–5	
12	N. W., 55	+	3	1	1941–48	0	1	1	Completely incapacitated for one year prior to prophylaxis; since then very active
					1948–49	Many	Almost weekly	0	
					1949–51	0	0	2	
					1951–52	1	0	1	
13	D. W., 54	0	3	1	1933–43	2–4	0	0	Given regular prophylactic colchicine and cinchophen elsewhere 1943–48 and had no attacks during this period; incapacitated for 6 months in 1949 after discontinuance of colchicine-cinchophen regimen; working regularly since resumption of colchicine prophylaxis
					1943–48	0	0	0	
					1948–49	Continuous attacks	0	0	
					1949–51	0	0	1	
					1951–52	0	0	0	
14	F. M., 62	++	3	1	1919–44	0	1	1	Did well on regular prophylaxis; took colchicine irregularly 1947–50; free of attacks to 1949; frequent recurrences in 1950
					1944–47	0	0	0	
					1947–49	0	0	0	
					1949–50	0	3	4	
15	L. G., 54	0	3	0.5	1946–49	1	0	1	Attacks before prophylaxis were too few for evaluation
					1949–50	0	0	1	
					1950–52	0	0	0	
16	V. P., 60	++++	2½	1.5	1930–35	1	0	0	Disabled many years due to chronic diffuse joint pains, many acute attacks and numerous tophaceous deposits; started colchicine prophylaxis in 1937 before our observation period; attacks became less frequent, but chronic pain persisted; few acute attacks since 1949, and less chronic pain 1950–51; died 1951, infection
					1935–37	Many	Many	0	
					1937–49	Few	Few	0	
					1949–50	1	0	0	
					1950–51	0	0	3	

TABLE 1 (*Continued*)

Case No.	Case Name and Age	Tophi	Years of Prophylaxis	Daily Colchicine (mg.)	Course before and during Prophylactic Regimen* Years	Attacks/Year Severe	Moderate	Mild	Remarks
17	I. K., 42	++	2	1	1938–50	3–4	0	Many	Frequently incapacitated prior to prophylaxis
					[1950–51	0	0	3]	
					[1951–52	0	0	3]	
18	J. R., 40	0	2	0.5–1	1944–49	0	1–2	0	Same as Case 17
					1949–50	5	0	0	
					[1950–51	0	0	2]	
					[1951–52	0	1	0]	
19	A. G., 61	++++	2	1	1932–38	0	6	6	Crippled and disabled for 7 or 8 years due to chronic pain and stiffness, recurrent acute attacks and extensive tophaceous deposits; now works regularly since prophylactic regimen and prolonged uricosuric medication
					1938–42	3	3	0	
					1942–50	4–6	0	0	
					[1950–51	0	0	2]	
					[1951–52	0	0	2]	
20	R. B., 72	++++	2	0.5 q. 2.d.	1928–48	Many	0	0	Incapacitated during winter months for many years but not for the two winters under observation on prophylaxis
					[1948–50	0	0	Few]	
21	G. B., 64	++++	2	1	1936–45	2–3	0	Many	Disabled many years by chronic diffuse pain, many acute attacks and numerous tophaceous deposits; infrequent acute attacks and much less chronic joint pain and stiffness since prophylaxis initiated
					1945–50	0	2–3	Many	
					[1950–51	0	0	4]	
					[1951–52	0	1	0]	
22	M. K., 70	++++	2	1	1914–25	Few	0	0	Like Case 16, but less satisfactory response
					1925–35	Many	0	0	
					1935–49	Few	Few	0	
					[1949–51	1	0	1]	
23	A. R., 42	0	2	1	1944–50	Few	Few	Every 1–2 weeks	During the first year results of prophylaxis unsatisfactory: many attacks. Spectacular results second year; no obvious explanation
					[1950–51	3	4	3]	
					[1951–52	0	0	0]	
24	A. L., 66	0	2	0.5	1930–49	0	1	0	Results of prophylaxis satisfactory; one attack in 1952 followed omission of cholchicine
					1949–50	2	0	1	
					[1950–51	0	0	0]	
					[1951–52	0	1	0]	
25	M. R., 64	+	2	0.5	1945–50	0	0	2–3	Mild gout; evaluation difficult
					[1950–51	0	0	0]	
					[1951–52	0	1	0]	
26	M. S., 59	0	2	1	1947	0	1	0	Control of acute attacks by prophylaxis incomplete; benefit problematic
					1947–49	0	0	0	
					1949–50	1	1	4–5	
					[1950–51	1	1	0]	
					[1951–52	1	1	1]	
27	I. K., 57	+	1½	0.5 q. 2.d.	1923–43	0	1–4	0	Chronic diffuse joint pain, numerous acute attacks incapacitated him prior to prophylaxis; pain controlled shortly after prophylaxis was begun; he has been working since
					1943–50	0	0	Numerous	
					[1950–51	0	0	3]	
					[1951–52	0	0	2]	
28	C. Y., 74	+	1½	0.5	1947–50	0	2	0	Chronic diffuse joint pain disappeared with prophylaxis
					[1950–52	0	1	0]	
29	H. W., 68	+	1½	0.5	1947–49	0	0	1	Same as Case 28
					1949–50	1	0	0	
					[1950–52	0	0	0]	
30	A. L., 45	0	1½	0.5	1948–50	1	1	0	Attacks before prophylaxis were too few and prophylactic regimen too short for evaluation
					[1950–51	0	0	0]	
					[1951–52	0	1	0]	
31	H. N., 47	0	1½	0.5	1948–49	0	1	0	Same as Case 30
					1949–50	0	0	2–3	
					[1950–52	0	0	2]	

* Figures not enclosed in brackets, before prophylaxis; those enclosed in brackets, during prophylaxis.

another day or two, depending upon response. The dosage is then slowly tapered off to 20 mg. a day, the treatment schedule being adjusted to individual requirements. If the suppressive effect of ACTH is terminated too soon, symptoms may reappear in the manner observed in many other disorders, a phenomenon interpreted by some as precipitation of a new attack due to corticoid-lack. It is advantageous to ensure against exacerbation by giving 1 to 2 mg. colchicine[29] or 0.6 to 0.8 gm. phenylbutazone daily concurrently with the tapering off of ACTH therapy and to continue administration of these drugs in this dosage for some time after subsidence of the acute symptoms.

TABLE II
CLINICAL RESPONSE TO ACTH THERAPY IN FORTY ACUTE GOUTY ATTACKS IN THIRTY-THREE SUBJECTS

Type of Response	No.	Per cent
A. Complete remission within 24–48 hr.	24	60
B. Good initial response, relapse after cessation of ACTH (inadequate treatment?)	4	10
C. Delayed response, complete remission within one week; dosage of 150–200 mg./day	4	10
D. Unsatisfactory response with dosage not more than 100 mg./day	4	10
E. Unsatisfactory response in spite of dosage to 200 mg./day	4	10

Our experience with intravenous use of aqueous ACTH is still too limited to determine whether this method of administration offers any distinct advantage; thus far no striking difference is apparent. The use of long-acting ACTH in repository gel form, as particularly recommended by Wolfson et al.[30] who were able to terminate twelve of thirteen acute attacks with a single injection containing 100 mg. ACTH, represents a marked simplification of treatment. We have found this method entirely adequate to abort incipient seizures but do not have enough experience with it as yet to determine whether it will be sufficient to control fulminating gouty arthritis.

Because of the short duration of ACTH therapy required for cessation of acute gouty attacks, significant side reactions are infrequent. On one occasion we were obliged to terminate treatment because of the development of congestive failure in a precariously compensated patient. Caution is necessary if there is a history of peptic ulcer. Mild changes in mood, chiefly elevation, are a common occurrence.

PHENYLBUTAZONE (BUTAZOLIDINE)®

Phenylbutazone is a potent analgesic and antiphlogistic agent, non-specific for acute gout but more effective, in our experience, in controlling the local and systemic manifestations than such drugs as salicylates or neocinchophen. We have employed it to terminate established attacks of acute gouty arthritis, to abort incipient seizures and to suppress lingering joint pains and stiffness in chronic gout. Our experience with the use of phenylbutazone is still limited but the simplicity of treatment, the rapidity of subjective relief in most cases, and the infrequency of residual discomforts thus far would seem to make it the drug of choice in many instances. Phenylbutazone also rapidly and sharply lowers serum urate levels and usually increases urinary excretion of urate[4] but we have not investigated its protracted regular use as a uricosuric or prophylactic agent because its safety for long-term administration has not been adequately established.

Kuzell et al.[31] reported complete remission within forty-eight hours in twenty-five of forty-eight attacks of acute gout; in fifteen cases there was a rapid decrease of signs and symptoms within forty-eight hours but some persistence up to seven days; in eight instances the response was limited to minor decrease in pain and swelling of the affected joint. We have thus far treated twenty acute attacks in sixteen patients, giving 0.8 gm. phenylbutazone daily in four divided doses by mouth. (Table III.) In thirteen attacks involving twelve patients remission was complete or virtually complete within twenty-four to forty-eight hours; in three of these cases the attacks had proved refractory to colchicine or ACTH and, indeed, the response in most members of this group was more rapid than in previous attacks treated with colchicine or ACTH. In seven attacks involving six patients there was improvement but it was slower; in four of these instances there was some residual pain, swelling and stiffness after a total dosage of 4.0 gm. in five days. In one instance these symptoms vanished quickly after a single 50 mg. dose of ACTH.

The limiting factor in the use of phenylbutazone is its toxicity. Gastric irritation, reactivation of healed peptic ulcer, drug rash

TABLE III

RESULTS WITH PHENYLBUTAZONE IN THE TREATMENT OF TWENTY ATTACKS OF ACUTE GOUTY ARTHRITIS IN SIXTEEN SUBJECTS (DOSAGE 0.8 GM./DAY IN FOUR DIVIDED DOSES)

Case		Known Duration of Gout (yr.)	Acute Attack					Response
				Severity				
No.	Name and Age		Location	Pain	Swelling	Redness	Duration (days)	
1	J. F., 47	12	Knee	+++	++	+	23	Took colchicine to diarrhea without relief; complete subsidence with 1.2 gm. phenylbutazone in 36 hours in both attacks
2	J. F.		Wrist	++	++	+	5	
3	P. C., 58	30	Hand	++	++	+	21	Attack refractory to colchicine; virtually complete subsidence after 0.8 gm. phenylbutazone in 24 hours
4	H. S., 50	6	Feet, knee	+++	++	++	Many weeks	Continued pain and swelling after colchicine and ACTH (200 mg daily); phenylbutazone 0.8 gm./24 hours brought complete relief
5	H. F., 44	19	Feet	+++	+++	+++	3	First attack brought under control after 2.4 gm. phenylbutazone in 3 days; second attack after 1.6 gm. phenylbutazone in 2 days; previous attacks treated with ACTH and/or colchicine usually lasted longer
6	H. F.		Big toe, hand	++	+	+	1	
7	D. R., 36	9	Ankle	++	±	+	3	Previous attacks required ACTH to 200 mg./day for 5–7 days for control; this attack subsided completely after 1.6 gm. phenylbutazone in 48 hours
8	M. S., 59	5	Knee	++	+	0	1	Previous attacks lingered for a long time after colchicine or ACTH therapy; this attack was smoothly aborted by 1.6 gm. phenylbutazone in 48 hours
9	R. C., 56	17	Hand	++	+	+	1	Uneventful, rapid recovery after 0.8 gm. phenylbutazone in 24 hours
10	J. M., 55	5	Big toe	+++	++	++	2	Attack over after 0.8 gm. phenylbutazone in 24 hours
11	M. D., 58	20	Knee	+	+	+	4	Pain subsided after 0.8 gm. phenylbutazone in 24 hours; complete relief after 1.6 gm. in 2 days
12	I. K., 42	15	Finger, big toe	++	+	+	6	Attack over after 1.2 gm. phenylbutazone in 36 hours; response about the same to colchicine
13	C. Y., 74	5	Finger	+	+	+	22	Lingering pain and tenderness terminated by 0.8 gm. phenylbutazone in 24 hours

TABLE III. (*Continued*)

Case		Known Duration of Gout (yr.)	Acute Attack					Response
				Severity			Duration (days)	
No.	Name and Age		Location	Pain	Swelling	Redness		
14	G. W., 46	12	Ankle	+	+	+	1	First attack aborted with 1.2 gm. phenylbutazone in 36 hr.; in second attack pain and redness promptly subsided but marked swelling persisted after 1.0 gm. phenylbutazone/24 hours; prompt subsidence after 50 mg. ACTH
15	G. W.		Knee	+	+++	+	1	
16	S. F., 35	11	Ankles	+++	+	+	1	Previous attacks incompletely controlled by colchicine or ACTH; partial response to 0.8 gm. phenylbutazone in 24 hours but slight pain for 2 weeks despite continued therapy
17	A. L., 45	3	Big toe	++	+	+	5	Partial response to 1.0 gm. phenylbutazone in 30 hours but stiffness persisted for several weeks
18	B. R., 56	12	Ankle	+++	++	++	2	Partial response in both attacks to 1.6 phenylbutazone in 2 days but vague pain persisted for 2 weeks despite continued medication for 5–6 days
19	B. R.		Big toe	+++	+++	++	2	
20	R. C., 48	21	Hand, wrist	+++	++	+	4	Pain diminished after 0.4 gm. phenylbutazone and completely gone after 1.6 gm. in 2 days; however, swelling became more marked and persisted until medication was stopped

and fever, anemia, salt and water retention with edema, and significant bone marrow depression have been reported to occur. In the short-term therapy of acute gout, however, these hazards appear to be inconsiderable; we were not obliged to interrupt treatment in our small experience to date. Vigilance, however, is essential.

PROBENECID (BENEMID)®

Probenecid has no definite analgesic or antiphlogistic action in man and is of no value in the treatment of acute gouty arthritis; whether prolonged administration will have any distinct prophylactic effect remains to be determined. The sole indication for use of probenecid in chronic gout, at present, is as a uricosuric agent. As such it is exceedingly potent. A single orally administered 2 gm. dose rapidly increases urate clearance, to a mean peak approximately fourfold, as a result of marked and highly selective suppression of tubular reabsorption of urate;[13] this uricosuric effect persists for some twenty-four hours. The mean daily increase in urinary urate excretion in the first week of administration is 46 per cent to 67 per cent, depending upon dosage.[32,33] A rapid and sharp decline in serum urate, to almost half of the pre-medication level with appropriate dosage, usually ensues and serum urate concentrations approaching the normal can ordinarily be maintained, apparently indefinitely, by continued dosage.[22,32–35] In effective uricosuric dosage levels the incidence of significant side reactions and toxicity appears thus far to be so low as to make protracted daily administration entirely

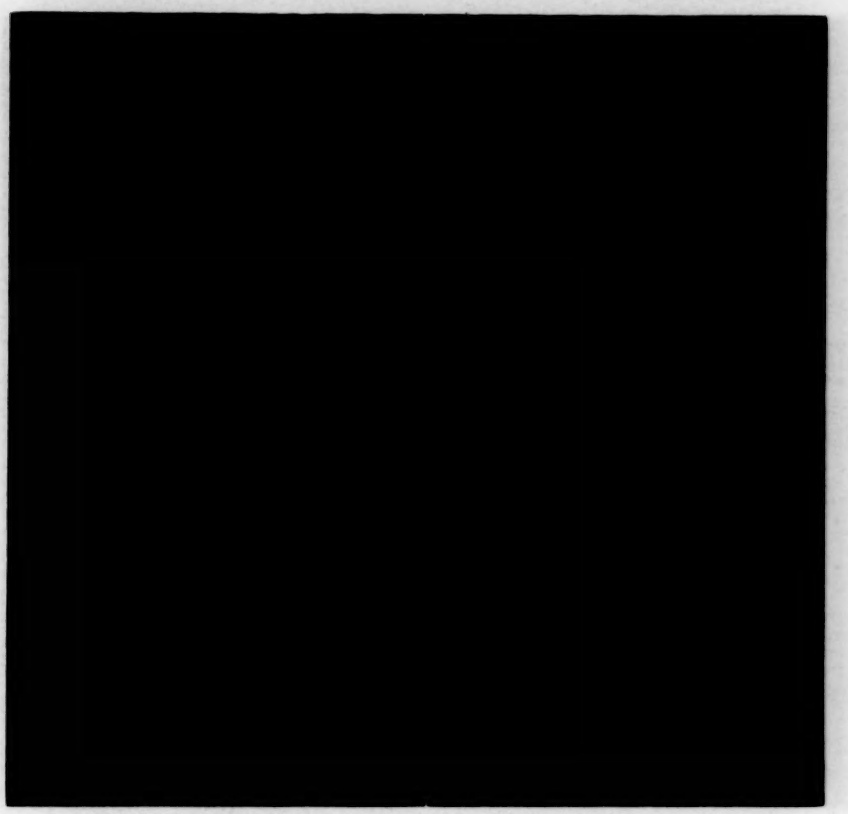
feasible.[32–36] In this respect probenecid was found to be distinctly superior to salicylates, carinamide, cinchophen and its derivatives, ACTH and other uricosuric agents we have tested.[4]

By reason of conservatism in the use of a new drug of unknown long range toxicity, it is our present policy to reserve regular administration of probenecid for those patients with chronic gout who have already developed tophi, persistent stiffness of the joints or other indication of clinically significant deposition of urate in the tissues. We have had forty such patients on a regular daily regimen of probenecid for periods of six months to two years; this is usually combined with regular colchicine prophylaxis and a restrictive diet. The optimum dose ordinarily is in the range of 1.0 to 2.0 gm. by mouth daily, the individual dosage depending upon several factors. The first is the degree of uricosuric response obtained, as measured by the effect on urine and serum urate on a constant low purine, low fat, restricted protein (50 to 80 gm./day) diet, as compared with control premedication levels on the same diet. The second is the objective of uricosuric therapy: if this is prophylactic, to prevent new tophi from forming, the minimum effective dosage is employed, usually 0.5 to 1.0 gm.; if it is intended to mobilize established deposits as expeditiously as possible, the maximum tolerated dosage is employed, usually 2.0 to 3.0 gm. Other factors entering into considerations of dosage are (1) the latitude of diet, larger doses being employed to cover more generous intake of urate precursors, much in the manner of the use of insulin in diabetes; (2) the degree of renal damage, larger doses often being required to produce and maintain significant uricosuria and satisfactory serum urate levels in the face of severe renal impairment; (3) allergic reactions to the drug, which may require reduction of dosage or complete withdrawal of the drug (two of our cases). When there is a history of urate calculi or the uricosuric response is unusually marked, small doses are employed, with caution, together with large fluid intake and an alkalinizing salt; and in general a high intake of fluids is recommended. A tendency to provoke acute attacks in the first days or weeks of probenecid administration should be taken into account. Salicylates should not be given concomitantly with probenecid because the uricosuric effect is nullified.[33,35]

Although lowered serum urate levels ordinarily can be maintained apparently indefinitely by continued probenecid administration, the uricosuric effect is demonstrable, on a fixed diet, only so long as mobilizable urate stores remain in the body. The quantity of excess urate initially present in the tissues and extracellular fluid therefore largely determines the duration of response. In normal subjects this is a matter of only a day or two; in less advanced tophaceous gout a significant increase in urinary urate excretion above control premedication levels is obtained for weeks or months; in more severe cases this persists for months or years.[25,35] It is our present practice to interrupt probenecid administration temporarily when the mobilizable body stores are depleted—just as mercurial diuretics are discontinued temporarily when the mobilizable edema fluid of tissues is exhausted.

To date we have observed ten patients with tophaceous gout in whom new tophi had appeared with some regularity in prior years and in no instance over periods of six months to two years have new tophi developed or old tophi significantly increased in size once the treatment was fairly instituted and so long as it was regularly maintained. Indeed, the indications are that tophaceous deposits can be extensively, if slowly, mobilized by such a regimen. This is evident from the quantity of excess urate recovered in the urine (more than 100 gm. in one case so far), the general relaxation of joint stiffness, swelling and disability in chronic gouty arthritis,[33,35] the drying up of fistulating and discharging tophi, the shrinkage and occasional complete disappearance of visible tophi[25,37] and, in roentgenograms, the diminution in size of soft tissue shadows attributable to urate deposits. Figures 1 and 2 illustrate the most striking success we have had in this respect so far, chiefly by use of large doses of salicylates.[37]

A pertinent question in connection with such use of probenecid relates to its long-term effects on the gouty kidney. So far, apart from fleeting colic due to flooding of the collecting ducts with urate as a result of overzealous dosage coupled with inadequate intake of fluids and alkali, no deleterious effects such as increase in serum nonprotein nitrogen, albuminuria or urinary excretion of formed elements have been observed. The suppression of tubular transport mechanisms for urate is transient and apparently wholly reversible, ceasing altogether within a day or two of discontinuance of the drug. Probenecid may, in fact, have some beneficial effect on the



1A 1B

FIG. 1. Case A. G. A, before treatment; B, after one year of regular uricosuric therapy, for the most part with 5 gm. salicylates daily.

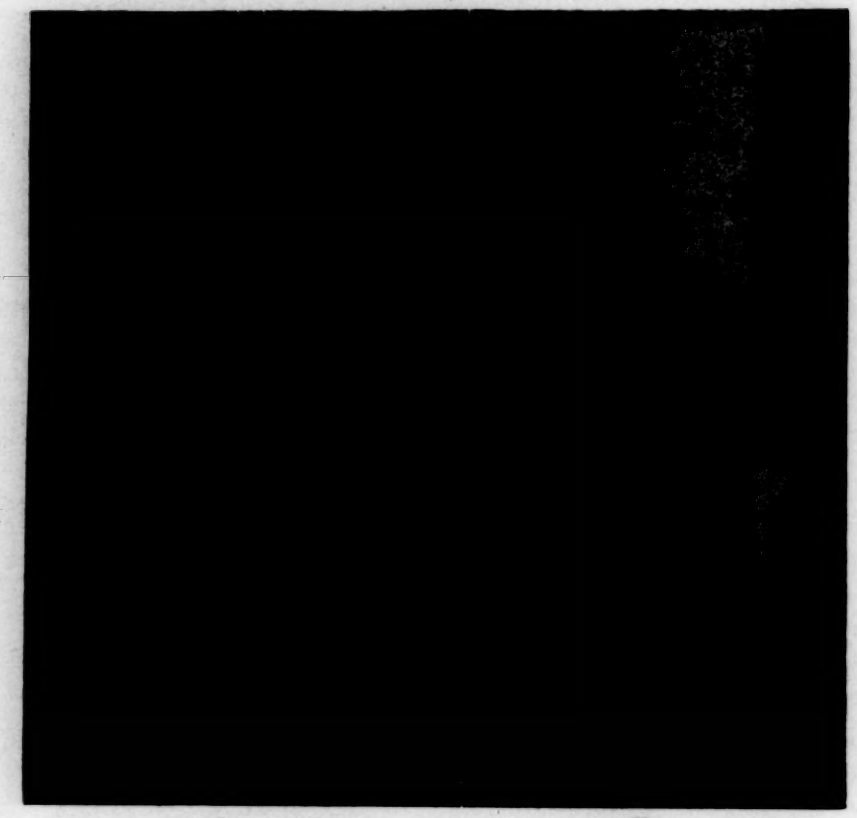
gouty kidney inasmuch as urate deposits may be mobilized from the kidneys as well as elsewhere; and diminution of tubular reabsorption of urate, while placing an extra load on the collecting tubules, should diminish the possibility of proximal tubular damage and interstitial infiltration. In regard to bone marrow depression and hepatotoxicity, no significant damage has yet been reported.

DIETARY RESTRICTION IN GOUT

It is impossible to contain purine formation completely by manipulation of the diet alone, since uric acid and other purines are elaborated for the most part by biosynthesis from simple nitrogen and carbon precursors derived from dietary proteins, fats and carbohydrates, as well as by degradation of preformed purines. Nevertheless, the composition of the diet is an important factor in regulating the magnitude of purine formation and excretion, and is therefore a significant consideration in management.

Ingestion of purine-rich foods markedly increases the purine load, as indicated by enhanced urinary excretion of urate in normal and gouty subjects (as much as 100 per cent if taken in large amounts) and by significant elevation of the serum urate. Meats, fish and fowl, if taken in sufficient quantity, also cause an appreciable rise in urate production, in part due to their content of preformed nucleotides. Nitrogen sources free of preformed purines contribute significantly less to urate formation but the effect is distinct if given in large amounts.[38] Diets high in fat but low in carbohydrate and protein also influence purine metabolism but chiefly at the renal level, causing a sharp decline in urinary urate excretion with a concomitant rise in serum rate.[39,40] High carbohydrate diets cause little or no measurable increase in urinary urate excretion.

In applying these basic facts to the regulation of diet in gout there is, as in the case of drugs, a dichotomy of purpose. One objective is to avoid precipitation of acute attacks, insofar as these are attributable to dietary indiscretions; the other is to minimize, as much as possible, the general trend toward insidious deposition of



2A 2B

FIG. 2. Case A. G. A, before treatment, showing large urate deposits in soft tissues at base of great toe, with "punched out" areas; B, marked diminution of urate deposits in the soft tissues and some sclerosis of "punched out" areas.

urate in the tissues. The two objectives cannot be wholly dissociated, of course, but they are not identical in principle or in practice. In both instances judgment as to the efficacy of dietary regulation is exceedingly difficult.

From time immemorial, overindulgence in food and alcohol has been regarded as a precipitating cause of acute gouty arthritis, and with good reason. Certainly consistent with this view is the sharp decline in overt gout noted in England and on the Continent in association with wartime and post-war austerities. Most of our own patients are quite convinced that avoidance of foods rich in purines and fats, more or less complete abstinence in regard to alcoholic beverages, and limitation of intake of protein in the form of meat, fish or fowl do decrease the number and severity of attacks. On the other hand, frugal living is by no means always necessary and, indeed, some of our patients flout every regulation with apparent impunity. Moreover, our experience with really rigorous restriction of purines, proteins and fats in gout, for example by means of the Kempner rice-fruit regimen, would indicate a marked decline in but not complete suppression of seizures. It seems clear that the diet is only one of a host of factors involved, albeit an important one, and that, until more is known about the true underlying causes of acute gouty arthritis, dietary management as a prophylactic measure must be empirical and should be varied according to individual requirements and tolerances. Obviously, gluttony should be discountenanced. When specific dietary or alcoholic inciters of acute seizures are alleged, they are proscribed. Beyond this no rules can be said to be established. Our own policy at present is to begin with a more restrictive diet than some advise and may be necessary; in patients with a history of frequent recurrence of acute attacks this is coupled with regular colchicine prophylaxis as already described. The diet is then liberalized according to events. Patients soon establish their own level of dietary forbearance. In general, this is more Spartan than might be supposed.

When the principal objective of dietary regulation is to minimize deposition of urate in the

TABLE IV

EFFECT OF INCREASED PROTEIN INTAKE ON URINARY AND SERUM URATE LEVELS IN EIGHT GOUTY AND TWO NON-GOUTY INDIVIDUALS

Case		Known Duration of Gout (yr.)	Tophi	Renal Status			Urinary Uric Acid (mg./24 hr.)		Serum Urate (mg. %)		Remarks
No.	Name and Age			Proteinuria	Serum NPN (mg. %)	% PSP Excretion (2 hr.)	Basal Diet	Increased Protein Diet	Basal Diet	Increased Protein Diet	
1	L. C., 42	2	0	0	33	..	812	1305	9.0	8.8	Basal diet: 70 gm. protein, no meat; added large meat portions twice daily for 2 weeks, protein intake about 140 gm./day; good renal function so that increased protein intake markedly increased the urinary urate excretion without increase in serum urate
2	D. R., 36	9	0	0	34	..	689	990	10.3	10.5	Basal diet: 70 gm. protein, no meat; for 2 weeks increased protein intake to 110 gm. a day without addition of meat; increase in vegetable and milk protein intake increased the urinary urate excretion moderately; good renal function, no increase in serum urate
3	D. R., 29	2	0	0	34	60	667	1000	6.8	9.4	Basal diet: 50 gm. protein, no meat; added large meat portions twice daily for weeks, protein intake about 140 gm. /day; in spite of good renal function, retention of urate in the serum occurred following prolonged high protein intake
4	F. E., 29	3	0	0	40	60	522	622	8.0	9.2	Basal diet: 70 gm. protein, no meat; added moderate meat portions once daily for weeks, protein intake about 100 gm./day; in spite of good renal function, the increased urate excretion could not counterbalance the increased protein intake, resulting in increase of serum urate level
5	O. G., 49	5	0	+ to ++	45	50	380	620	10.0	9.8	Basal diet: 60 gm. protein, no meat; added moderate meat portions once daily for 1 week, protein intake 100 gm. /day; the increased protein intake apparently was well disposed of by increased excretion without increase in serum urate level, despite some renal damage (proteinuria)
6	V. P., 60	20	++++	Trace	62–92	33	198	202	10.5	11.0	Basal diet: 60 gm. protein, no meat; added moderate meat portions once daily for a few days, protein intake about 100 gm./day; renal damage (nephrosclerosis); no increase in urinary urate excretion, slight rise in serum urate
7	M. K., 68	35	++++	Trace	40	34	810	852	....	....	Diet same as Case 6; marked proteinuria; increased protein intake did not cause further increase in uric acid excretion, serum urate not determined
8	G. B., 64	16	++++	++to+++	59	39	...	.....	8.4	9.6	Basal diet: 50–60 gm. protein, no meat; ate a big steak the previous evening; serum urate increased significantly; patient also had hypertensive cardiovascular-renal disease
9	E. B., 32	..	.....	.....	..	..	400	552	....	...	Normal healthy subject; basal diet: protein 40 gm., no meat; increased protein intake to 80 gm. per day, without adding meat, for 2 weeks; (cf. Case 2)
10	D. S., 50	..	.....	.....	..	..	530	726	4.1	4.2	Chronic rheumatoid arthritis with normal renal function; same diet as Cases 5, 6 and 7; increased urinary excretion of uric acid without rise in serum urate level

tissues in tophaceous gout, we begin with a more restrictive basic diet low in purines, poor in fat and limited in proteins (50 to 75 gm./day). This consists chiefly of cereals, grain products, eggs, cheese, milk, non-leguminous vegetables and fruits; but in most instances the basic diet

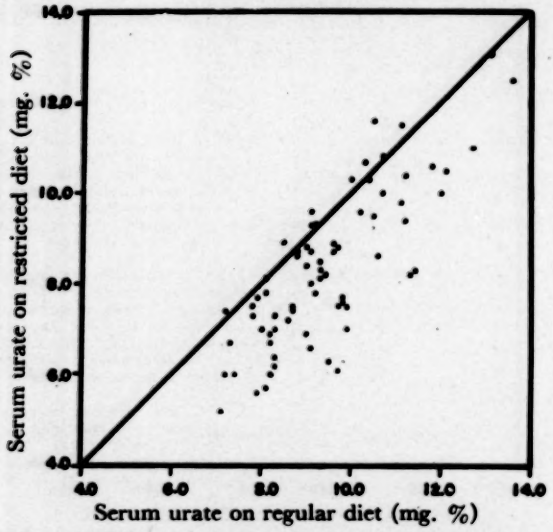


FIG. 3. Effect of dietary restriction (low purine, low fat, protein limited to 50 to 75 gm./day) on serum urate levels in seventy-one gouty subjects. Points falling below the "no change" diagonal reflect a decline in serum urate level in the amount indicated by reference to figures on abscissa and ordinate.

can subsequently be liberalized somewhat, particularly if uricosuric agents are regularly administered, by addition of small portions of meats, fish or fowl several times each week, occasionally once daily. The effects of such a diet on the rate of urate deposition in the tissues cannot be measured directly by ordinary methods but are reflected in the urinary urate excretion and in the serum urate level. The urinary urate excretion shows a decline of about 200 to 300 mg./twenty-four hours. Serum urate levels show a general downward trend (Fig. 3), the mean fall being 1.2 mg. per cent, with declines in excess of 3 mg. per cent in occasional instances. The evidence, while indirect, implies a modest but significant lowering of urate production. Conjoint use of a uricosuric agent, however, makes for much more effective negative urate balance.

The efficiency of the kidneys in clearing urate from the plasma plays a decisive role in determining the effect of diet on urate balance. If the extra urate load resulting from dietary excesses can be excreted in its entirety, none is retained in the tissues; if not, the extracellular fluid content of urate rises (Table IV) and that portion of the extra load not excreted presumably is largely deposited in the tissues. It is to the steady accumulation of such increments over the years that development of the deformities and disabilities of chronic gouty arthritis may be ascribed.

SUMMARY

1. Present knowledge concerning the fundamental nature of the gouty trait, the causes of acute gouty arthritis and the pathogenesis of chronic tophaceous gout, is reviewed.

2. The regulation of gout involves two more or less distinct problems: (1) prevention and suppression of attacks of acute gouty arthritis, which are not attributable to urate *per se* but to unknown causes; (2) prevention and mobilization of tophi, which represent excessive urate deposition in the tissues. Each problem requires specifically oriented management. Current principles of such management are outlined.

3. The three uses of colchicine, to terminate established attacks of acute gouty arthritis, to abort impending attacks, and as a prophylactic agent to prevent seizures in intercritical periods, are described and the results of each usage analyzed. The advantages of regular colchicine prophylaxis are stressed.

4. The use of corticotropin (ACTH) in acute gouty arthritis is described and the results in forty cases are presented. ACTH is usually effective if given in adequate dosage properly scheduled.

5. The use of phenylbutazone (butazolidine) in acute gouty arthritis is described and the results in twenty cases are presented. Administration is simple and relief is rapid and effective in most cases. Toxicity is low in short-term therapy.

6. The use of probenecid (benemid) as a uricosuric agent in chronic tophaceous gout is described. Experience with forty gouty subjects given daily dosage for six months to two years indicates that formation of new tophi and enlargement of old tophi can be prevented. Urate deposits in the tissues can be mobilized, with relief of chronic joint disability and shrinkage of visible tophi.

7. The conjoint use of restrictive diets to avoid precipitation of acute attacks and to minimize deposition of urate in the tissues is discussed.

Acknowledgments: We are greatly indebted to Sharp and Dohme, Inc., for a generous supply of probenecid and to Geigy Company, Inc., for making phenylbutazone available to us.

REFERENCES

1. Talbott, J. H. Serum urate in relatives of gouty patients. *J. Clin. Investigation*, 19: 645, 1940.
2. Smyth, C. J., Cotterman, C. W. and Freyberg, R. H. The genetics of gout and hyperuricemia—an analysis of nineteen families. *J. Clin. Investigation*, 27: 749, 1948.
3. Stecher, R. M., Hersh, A. H. and Solomon, W. M. The heredity of gout and its relationship to familial hyperuricemia. *Ann. Int. Med.*, 31: 595, 1949.
4. Yü, T. F. and Gutman, A. B. Unpublished data.
5. Benedict, J. D., Roche, M., Yü, T. F., Bien, E. J. Gutman, A. B. and Stetten, DeW., Jr. The incorporation of glycine nitrogen into uric acid in normal and gouty man. *Metabolism*, 1: 3, 1952.
6. Sonne, J. C., Buchanan, J. M. and Delluva, A. M. Biological precursors of uric acid carbon. *J. Biol. Chem.*, 166: 395, 1946.
7. Greenberg, G. R. De novo synthesis of hypoxanthine via inosine-5-phosphate and inosine. *J. Biol. Chem.*, 190: 611, 1951.
8. Schulman, M. P. and Buchanan, J. M. Biosynthesis of the purines. II. Metabolism of 4-amino-5-imidazole-carboxamide in pigeon liver. *J. Biol. Chem.*, 196: 513, 1952.
9. Benedict, J. D., Wyngaarden, J. B., Bien, E. J., Yü, T. F., Gutman, A. B. and Stetten, DeW., Jr. Unpublished studies.
10. Talbott, J. H. Gout. New York, 1943. Oxford University Press.
11. Friedman, M. and Byers, S. O. Increased renal excretion of urate in young patients with gout. *Am. J. Med.*, 9: 31, 1950.
12. Sirota J. H., Yü, T. F. and Gutman, A. B. Unpublished studies.
13. Sirota, J. H., Yü, T. F. and Gutman, A. B. Effect of benemid (p-(di-n-propylsulfamyl)-benzoic acid) on urate clearance and other discrete renal functions in gouty subjects. *J. Clin. Investigation*, 31: 692, 1952.
14. Berliner, R. W., Hilton, J. G., Yü, T. F. and Kennedy, T. J., Jr. The renal mechanism for urate excretion in man. *J. Clin. Investigation*, 29: 396, 1950.
15. Smith, H. W. The Kidney, Structure and Function in Health and Disease. New York, 1951. Oxford University Press.
16. Robinson, W. D., Conn, J. W., Block, W. D. and Louis, L. H. Role of the adrenal cortex in urate metabolism and in gout. *Proc. Central Soc. Clin. Research*, 21: 23, 1948.
17. Hellman, L. Production of acute gouty arthritis by adrenocorticotropin. *Science*, 109: 280, 1949.
18. Gutman, A. B. and Yü, T. F. Effects of adrenocorticotropic hormone (ACTH) in gout. *Am. J. Med.*, 9: 24, 1950.
19. Levin, M. H., Fred, L. and Bassett, S. H. Metabolic studies in gout. *J. Clin. Endocrinol.*, 12: 506, 1952.
20. Wolfson, W. Q., Hunt, H. D., Levine, R., Guterman, H. S., Cohen, C., Rosenberg, E. F., Huddleston, B. and Kadota, K. The transport and excretion of uric acid in man. v. A sex difference in urate metabolism. *J. Clin. Endocrin.*, 9: 749, 1949.
21. Harkavy, J. Allergic factors in gout. *J. A. M. A.*, 139: 75, 1949.
22. Gutman, A. B. and Yü, T. F. Gout, a derangement of purine metabolism. *Advances Int. Med.*, vol. 5, 1951.
23. McCracken, J. P., Owen, P. S. and Pratt, J. H. Gout: still a forgotten disease. *J. A. M. A.*, 131: 367, 1946.
24. Benedict, J. D., Forsham, P. H. and Stetten, DeW., Jr. The metabolism of uric acid in the normal and gouty human studied with the aid of isotopic uric acid. *J. Biol. Chem.*, 181: 183, 1949.
25. Gutman, A. B. Some recent advances in the study of uric acid metabolism and gout. *Bull. New York Acad. Med.*, 27: 144, 1951.
26. Cohen, A. Gout. *Am. J. M. Sc.*, 192: 488, 1936.
27. Bartels, E. C. Successful treatment of gout. *Ann. Int. Med.*, 18: 21, 1943.
28. Hollander, J. L., Brown, E. M., Jr., Jessar, R. A. and Brown, C. Y. Hydrocortisone and cortisone injected into arthritic joints. *J. A. M. A.*, 147: 1629, 1951.
29. Wolfson, W. Q., Hunt, H. D., Cohn, C., Robinson, W. D. and Duff, I. F. ACTH and colchicine in the clinical treatment of acute gouty arthritis. Physiological considerations and review of therapeutic results in fifty-one attacks. *J. Michigan M. Soc.*, 49: 1058, 1950.
30. Wolfson, W. Q., Thompson, R. E., Robinson, W. D., Duff, I. F., Cohn, C., Lewis, L. and Hunt, H. D. The development, evaluation and clinical use of long-acting ACTH preparations. Proc. Second Clinical ACTH Conf., 2: 1, 1951.
31. Kuzell, W. C., Schaffarzick, R. W., Brown, B. and Mankle, E. A. Phenylbutazone (butazolidin) in rheumatoid arthritis and gout. *J. A. M. A.*, 149: 729, 1952.
32. Gutman, A. B. In Combined Staff Clinic on uric acid metabolism and gout. *Am. J. Med.*, 9: 799, 1950.
33. Gutman, A. B. and Yü, T. F. Benemid (p-(di-n-propylsulfamyl)-benzoic acid) as uricosuric agent in chronic gouty arthritis. *Tr. A. Am. Physicians*, 64: 279, 1951.
34. Talbott, J. H., Bishop, C., Norcross, B. M. and Lockie, L. M. The clinical and metabolic effects of benemid in patients with gout. *Tr. A. Am. Physicians*, 64: 372, 1951.
35. Pascale, L. R., Dubin, A. and Hoffman, W. S. Therapeutic value of probenecid (benemid) in gout. *J. A. M. A.*, 149: 1188, 1952.
36. Boyer, W. P. and Strickland, S. C. Benemid: preliminary assessment of its toxicity in man. Tr. Tenth Veterans Administration, Army-Navy Conference on the Chemotherapy of Tuberculosis, Atlanta, Georgia, 1951.
37. Yü, T. F. and Gutman, A. B. Mobilization of gouty tophi by protracted use of uricosuric agents. *Am. J. Med.*, 11: 765, 1951.
38. Mendel, L. B. and Brown, E. W. The rate of elimination of uric acid in man. *J. A. M. A.*, 49: 896, 1907.
39. Lockie, L. M. and Hubbard, R. S. Gout: changes in symptoms and purine metabolism produced by high fat diets in four gouty patients. *J. A. M. A.*, 104: 2072, 1935.
40. Adlersberg, D. and Ellenberg, M. Effect of carbohydrate and fat in the diet on uric acid excretion. *J. Biol. Chem.*, 128: 379, 1939.

Seminars on Gastrointestinal Physiology

Problems in Ulcerative Colitis*

THOMAS E. MACHELLA, M.D.
Philadelphia, Pennsylvania

CHRONIC idiopathic ulcerative colitis presents many problems and they concern practically every aspect of the disease. In this article those of its etiology and its therapy are discussed; also, the incidence of malignant degeneration and the nature of associated extracolonic disturbances, including pregnancy.

ETIOLOGY

Among the major hypotheses advanced to account for the development of idiopathic ulcerative colitis are: infection, deficiency of a specific intestinal factor, excess lysozyme production, damage to the colonic mucosa by small intestinal proteolytic enzymes, allergy and emotional disturbances.

Infection. The clinical picture, so frequently characterized by diarrhea and fever, as well as its pathologic characteristics strongly suggest an infectious etiology. It was natural, therefore, that attempts should be made to isolate a specific organism, and indeed a variety of bacteria, as well as other organisms, have been suspected as etiologic agents or at least of having some specific relationship. They include B. proteus, B. pyocyaneus, B. lactis aerogenes, B. mucosus capsulatus, B. morgani, B necrophorum, beta hemolytic colon bacillus, ameba, histoplasma and the fungus geotrichum, as well as a gram-positive diplococcus and the dysentery organisms. Of these the last two have stimulated the greatest amount of interest

The similarities between bacillary dysentery and this type of ulcerative colitis led to numerous attempts to establish a relationship. In 1921 Hurst[93] presented the view that ulcerative colitis is a chronic form of bacillary dysentery and, indeed, dysentery organisms have been isolated from some cases of idiopathic ulcerative colitis. A survey of the literature up to 1944 by Felsen[62] revealed that a form of B. dysenteriae had been isolated in from 2 to 60 per cent of the reported cases. In further support of a relationship between the two diseases Felsen[61] cited an 8.2 per cent incidence of chronic ulcerative colitis in 122 cases of bacillary dysentery. On the other hand, certain data would indicate that these diseases do not have a common etiology. These include isolation of a dysentery organism rarely,[24] or not at all,[83,91,185] in fairly large series of cases of ulcerative colitis; the lack of contagiousness of the disease (it is unusual to find more than one case in a family); and, in a sixteen year follow-up of 102 cases of bacillary dysentery by Brown and Bargen,[24] the discovery of only one case of ulcerative colitis.

The claim of Bargen that a gram-positive diplococcus[12] is the etiologic factor in this disease, particularly in the variety classified as type 1 "thrombo-ulcerative colitis," has not been generally accepted despite the fact that some workers[27,60] have been able to isolate the diplococcus from a variable number of patients. Rafsky and Mannheim,[163] who isolated the organism from 314 patients with miscellaneous diseases of the bowel, regarded it as a nonspecific enterococcus. Paulson[151] and also Bassler[16] were likewise able to isolate the organism from patients without, as well as with, ulcerative colitis. Hern,[91] Hurst,[94] Brown[25] and Gaither[65] and others regarded the diplococcus as a secondary invader. It would seem, therefore, that the etiologic role of the gram-positive diplococcus in idiopathic ulcerative colitis has not been established.

Deficiency Disease. The possibility that ulcerative colitis is a deficiency disease and that the responsible factor is the lack of an essential in-

* From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

gredient of gastrointestinal wall was proposed in 1945 by Gill.[66] He observed symptomatic improvement when he administered raw pig small intestine or a desiccated and defatted mucosal preparation. Others[85,192] also ascribed beneficial results to the administration of preparations of hog intestinal mucosa. However, other reports[40,86,102,106,193] of therapy with preparations of hog duodenum were discouraging and cast doubt on the possibility that a deficiency of a substance normally present in pig intestine is responsible for the ulcerative disease.

Ehrlick[56] suggested that chronic idiopathic ulcerative colitis is due to a deficiency of an antiproteolytic enzyme in the colon. Such a deficiency, he believed, predisposes the colonic mucosa to autolysis by proteolytic enzymes delivered to the colon by a hypermotile small intestine. In support of his idea he cited the subsidence of edema, inflammation, spasm and ulceration when a hog stomach preparation was administered. The preparation was believed to contain a protective or antiproteolytic enzyme. Erlick's idea is supported by the improvement which often occurs after ileostomy but does not explain satisfactorily the small intestinal involvement sometimes associated with the disease in the colon.

Lysozyme. The observation of an increased concentration of lysozyme in the stools led Meyer et al.[137] to suggest that this enzyme was of etiologic importance in the disease. It was postulated that lysozyme removed the protective surface mucus from the colon by virtue of its mucolytic activity and favored ulceration of the denuded mucosa by indigenous bacterial flora. An increased concentration of lysozyme in the stools of ulcerative colitis patients was confirmed by others.[71,168] Grace and his associates[71,72] furnished support to the hypothesis by showing striking and abrupt increases in the lysozyme titers of stools of such patients over short periods of time during anger, hostility, resentment and frustration, and prompt decreases with the onset of mental relaxation and calm. The above observations stimulated a series of experiments in which attempts were made to produce ulcerative lesions by the administration of lysozyme.

Meyer and his associates[138] noted ulcerative lesions of the upper gastrointestinal tract of dogs following the oral administration of large amounts of lysozyme (1,500 units or more per cc.). Their observations were confirmed by Prudden et al.[160] for the canine colon when lysozyme was administered orally as well as intra-arterially. Additional support for the lysozyme hypothesis was furnished by Grace et al.[71] who noted circumscribed areas of inflammation and edema on the prolapsed mucous membrane of a colostomy of a patient with ulcerative colitis following the application of human tears (600 units of lysozyme per cc.) for a period of twenty-four hours

Nickel et al.,[147] however, employing a somewhat different technic from that of Prudden et al.[160] were unable to confirm the latter's findings. They prepared isolated loops of colon in a manner similar to that of a colostomy in three dogs, instilled into them 4 to 5 cc. of a 10 per cent solution of lysozyme crystals in saline daily for a period of one to two weeks. Two other animals, prepared similarly, were given daily instillations of lysozyme plus material drained from the ileostomy openings of ulcerative colitis patients. In neither set of animals were persistent ulcerations observed. Although inflammation and superficial erosions were noted in both groups, they were transient and disappeared despite subsequent repeated instillations. Moeller et al.,[142b] furthermore, were not able to demonstrate any alterations in the mucous membrane of ileocolic pouches of dogs following prolonged exposure to high concentrations of lysozyme. They used much higher concentrations than those found in the feces of patients with severe ulcerative colitis.

Certain observations have suggested that the increased lysozyme content of the stools during the active phase of ulcerative colitis is corollary rather than etiologic. These include the finding of large amounts of lysozyme in granulation tissue,[158b] the demonstration of the ability of some bacteria to produce small amounts of lysozyme, and the evidence presented by Sammons[180] to the effect that the source of lysozyme in ulcerative colitis patients may be pus cells. Especially disturbing to the lysozyme hypothesis have been the observations of Glass et al.[69] who were not able to demonstrate any mucolytic action of lysozyme *in vitro* on colonic mucus, and who inferred that, whatever the consequences of increased lysozyme secretion in ulcerative colitis might be, they do not include digestion of the protective mucous coating of the colon.

The lack of spectacular beneficial therapeutic

results from the administration[139,168,213] of antilysoyme agents in ulcerative colitis likewise has failed to support an etiologic role for lysozyme. Furthermore, the administration of an aerosol detergent and the consequent decreased fecal lysozyme titer were not associated with any change in the clinical course of the disease in the experience of Reifenstein et al.[168]

Role of Pancreatic Enzymes. The possibility that proteolytic enzymes of the upper gastrointestinal tract might be of importance in the etiology was suggested by Portis et al.[155] who observed damage to the colonic mucosa of dogs following the instillation of a solution of 2 per cent trypsin into the colon. This possibility, however, has not been supported by such observations as: (1) failure to find any alterations in a loop of colonic mucosa transposed into the duodenum of dogs just beyond the ampulla of Vater over a period of time varying from two weeks to ten months,[113] (2) inability to demonstrate an increased pancreatic enzyme concentration of aspirated duodenal juice in thirteen patients with ulcerative colitis by means of a secretin test[113] and (3) the report[50] of ulcerative colitis developing in a patient with chronic relapsing pancreatitis of years' duration in whom the secretin test revealed a deficient pancreatic secretion.

Allergy. An etiologic role for allergy in ulcerative colitis was proposed by Andresen[4,5] and stressed by Rowe.[178,179] They based their opinion on the favorable results when food allergy was taken into consideration in the management of the disease. The allergy hypothesis received some support from the observations of Gray et al.[74,75] and Walzer et al.[206] which indicated that an atopic reagin may be located or fixed in the colonic mucosa to permit a specific antigen acting locally to produce an inflammatory reaction. Gray[76] as well as others have pointed out that a local bacterial allergy may be concerned.

The importance of food allergy in ulcerative colitis has been variously assessed. Andresen[5] believed food allergy was responsible in at least 66 per cent of his cases. Mackie[128] encountered allergic reactions to food in 60 per cent of 200 cases at one time or another in the course of the colitis. Bassler[17] found food allergy to be of significance in only about 20 per cent of his patients. Paulley[150] found a slightly higher incidence of those diseases regarded by some as allergic in the past histories of colitis patients and their families than among controls. He believed this could be expected in view of the belief by some that allergic disorders are conditioned by emotional factors. Kiefer[101] was not enthusiastic about his results with the Rowe diet prescribed for short periods, or with those following the administration of benadryl. Collins and Pritchett[31] did not find food allergy a common cause of the disease but found that allergic management was helpful.

It would appear that food allergy has not been established as the cause of ulcerative colitis, although most workers agree that food allergy can occur in the disease and that when it does it is of importance in the management of the patient.

Recently, Levine et al.[114] suggested that connective tissue lesions in the bowel strongly indicate that ulcerative colitis is a collagen disease, possibly related to the hypersensitivity state. The occurrence of arthritis, erythema nodosum and glomerulitis as complications were regarded as confirmatory. The occurrence of ulcerative lesions in the colon of patients with polyarteritis,[215] as well as in association with erythema multiforme[37] has been noted.

Role of the Psyche. The role of the psyche in ulcerative colitis was emphasized in 1930 by Murray[145] and shortly thereafter by Sullivan and Chandler.[195] Very little prominence was given to this factor during the era of the sulfonamides and advent of antibiotics; however, as the early enthusiasm attending the use of these agents was replaced by disappointment, increasing attention has been paid to the role of emotional factors.[8,41,44,45,46,78,79,98,116,129,148,156,161,162,184,186,196,214] Careful studies have revealed characteristic personality traits and impressive relationships between emotional stress and the onset of disease and the occurrence of relapses. Furthermore, the disease has responded to psychotherapy when other measures have failed. The results of skillful psychotherapy in the hands of Groen and Bastiaans[79] have been more impressive than those with many other therapeutic regimens not intentionally psychotherapeutic in approach.

Considerable support for the role of emotions has been furnished by observations on the appearance of the colonic mucosa in response to emotional states. In general it has been found that during phases of anger, resentment or hostility the mucosa becomes hyperemic, engorged and hyperactive, while during periods

of relative calm and tranquility it is pale and the bowel relatively inactive.[72,211] Pain, fear and anxiety produce pallor of the mucosa and inhibition of motility[211] while embarrassment causes flushing.[212]

The mechanism by which such emotional factors produce changes in the colonic mucosa of the ulcerative colitis patient is not clear. Certain observations, however, indicate that the autonomic nervous system is intimately concerned. That its parasympathetic division is involved is strongly suggested by the observation of changes similar to those reported for the human in response to anger, resentment and hostility[72,211] following stimulation of the parasympathetic nerve supply of the colon[68] of experimental animals or following administration of the parasympathomimetic drugs mecholyl,[210] acetyl choline and prostigmine.[117] Such observations suggest that parasympathetic influences are primarily excitatory to the bowel and when operative for prolonged periods, as in the case of mecholyl,[210] may produce changes similar to those found in the colon of the ulcerative colitis patient.

Certain observations, however, indicate that the sympathetic innervation of the colon also may contain excitatory effector fibers. For example, Schlitt et al.[182] found that neither sacral parasympathectomy nor vagotomy produced any detectable change in either the basic colonic motility or in the response of the colon to external stimuli such as pain and hunger. It was only after combined sympathectomy and sacral parasympathectomy that distinctly different wave patterns were observed. Their observations are in accord with the conclusions previously reached by Wells et al.[209] whose work cast doubt on the generally accepted antagonism of the two effector components of the autonomic nervous system in relation to the gastrointestinal tract. As a matter of fact, in some instances[68] stimulation of the sympathetics has produced predominantly motor responses. The reaction occurring in a colon as a result of emotional stimuli could therefore very well depend not only on the nature, intensity and duration of the stimulus but also on the relative influences of the two effector divisions of the autonomic nervous system. Thus, differences in stimuli and in the response of individuals might account for the occurrence of ulcerative colitis in one patient and of "spastic" or "irritable" colon in another.

THERAPY

In this section the results of treatment of ulcerative colitis with a variety of regimens are reviewed. They include the use of the sulfonamides, antibiotics, preparations of hog stomach and intestine, cortisone, corticotropin, psychotherapy and various miscellaneous agents.

Sulfonamides and Antibiotics. In view of the fact that infection in ulcerative colitis has been emphasized as of primary etiologic significance as well as being a secondary factor in maintaining and accentuating the disease, the advent of the sulfonamides and antibiotics suggested that they might be of value in treatment. The incidence of good results from sulfonamide compounds in 1,275 cases summarized in Table I is 57.7 per cent, and for antibiotics in the 167 cases contained in Table II is 61.6 per cent. The results are comparable in some instances to those obtained from measures not directed primarily at infection. The fact that they are not any better is not surprising in view of the fact that an infectious etiology in non-specific ulcerative colitis has not been established.

Some authors, accepting the fact that a bacterial etiology in ulcerative colitis has not been established, nevertheless persist in prescribing sulfonamides or antibiotics in its treatment. They do so in an attempt to depress the bacterial flora of the colon, believing that this may benefit the patient. The role of the bacterial flora of the colon in the maintenance or accentuation of the disease is difficult to assess. Certain data would indicate that it is not an important one. For, when appropriate bacteriologic studies are made there is a lack of correlation between changes in the fecal flora brought about by the various antibacterial agents and the clinical course of the disease.[18,150,174,187,216] Furthermore, careful studies such as those of Marshall et al.[133] have revealed that although the bacterial flora of the feces could be altered temporarily by sulfonamides, after a time it resembled that of the untreated patient in type and quantity. They also demonstrated that a fecal bacterial population resistant to the antibiotics developed more or less rapidly after continued administration.

On the basis of the data presented there would appear to be, in the opinion of the writer, little or no place for the use of sulfonamides or antibiotics in the management of ulcerative colitis unless a suppurative complication threat-

TABLE I

SUMMARY OF MAJOR REPORTS ON THE USE OF SULFONAMIDES IN THE TREATMENT OF ULCERATIVE COLITIS

Compound	No. of Reports	Total No. of Patients Treated	Good Results (%)	References
Neoprontosil	4	86	37	11, 21, 101, 188
Sulfanilamide	5	78	36	32, 43, 60, 101, 188
Sulfathiazole	3	85	40	19, 141, 188
Nisulfazole	3	87	65	130, 139, 213
Sulfadiazine	2	79	45	101, 141
Sulfaguanidine	7	215	44	3, 19, 29, 101, 105, 141, 187
Sulfasuxidine	5	260	64	19, 33, 38, 101, 188
Sulfaphthalidine	6	164	75	6, 14, 19, 101, 158, 188
Sodium phthalyl sulfacetamide	1	28	64	89
Salazopyrine	4	193	77	15, 92, 144, 198
Total	40	1,275	57.7	

TABLE II

SUMMARY OF MAJOR REPORTS ON THE USE OF ANTIBIOTICS IN THE TREATMENT OF ULCERATIVE COLITIS

Antibiotic	No. of Reports	No. of Patients Treated	Good Results (%)	References
Penicillin (intramuscular)	10	37	43	10, 19, 36, 51, 81, 84, 100, 101, 110, 122
Penicillin (oral)	1	45	100	191
Streptomycin	9	42	31	19, 35, 39, 48, 101, 104, 115, 216
Aureomycin	1	13	54	132
Chloramphenicol	1	24	67	18
Tyrothrycin	1	6	100	190
Total	23	167	61.6	

TABLE III

SUMMARY OF RESULTS OF THE USE OF PREPARATIONS OF HOG STOMACH AND INTESTINE IN ULCERATIVE COLITIS

Author	Preparation of Hog's	No. of Patients Treated	Good Results (%)	Author's Opinion of Results
Ehrlick, 1950	Stomach	24	81	.....
Gill, 1945	Small intestine	10	70	.....
Haskell and Friedman, 1948	Small intestine	27	48 to 89	.....
Streicher, 1950	Duodenum	43	35 to 79	.....
Crohn, 1950	Duodenum	Small	.....	Rather disappointing
Haskell, 1950	Duodenum	38	.....	Disappointing
Kiefer, 1950	Intestine or duodenum	Small	.....	Not impressed
Kirsner, 1950	Duodenum	Small	.....	Results were nil

ens or exists. Their unrestricted use may even be deleterious as they may cause undesirable side effects. Recently, aureomycin and terramycin[80] have been observed to cause colitis severe enough to resemble ulcerative colitis clinically, sigmoidoscopically and roentgenologically.

TABLE IV
SUMMARY OF RESULTS OF TREATMENT OF ULCERATIVE COLITIS WITH ANTI-LYSOZYME AGENTS

Author	Agent	No. of Patients Treated	Good Results (%)
Major, 1946	Nisulfazole	37	91
Wills, 1949	Nisulfazole	24	60
Meyer and Prudden, 1949	Nisulfazole	26	65
Prudden, 1950	Sodium hexadecyl-sulfate	18	66
Reifenstein et al., 1950	Aerosol detergent	6	0
Lobstein et al., 1952	RD 11	10	30
Total		121	65.9

Preparations of Hog Stomach and Intestine. The results of administration of various preparations of hog stomach and intestine in ulcerative colitis patients are summarized in Table III. Favorable responses were obtained in from 52 to 81 per cent of 104 cases depending on the criteria used in judging the effectiveness of therapy. The results obtained when a preparation of hog duodenum was administered were disappointing. (Table III.) Whereas mild cases were seemingly benefited, no improvement was observed in those who were moderately or severely ill.[86,193]

Anti-lysozyme Agents. Results from the administration of various anti-lysozyme agents are summarized in Table IV. In a total of 121 cases treated the incidence of "good" results was 65.9 per cent. Such an incidence is about what would be expected from any form of nonspecific therapy.

Corticotropin and Cortisone. The occurrence of joint manifestations and erythema nodosum in some ulcerative colitis patients led to the trial of cortisone and ACTH in the disease. Additional rationale for expecting that the compounds might be beneficial includes the finding of decreased urinary excretion of 17-ketosteroids indicating a low level of adrenal activity.[157,169] A summary of the recorded cases treated with cortisone is contained in Table V and with ACTH in Table VI. Good results were obtained in 44 per cent of twenty-five patients treated with cortisone and in 67.5 per cent of 117 cases treated with ACTH. The data appear to indicate that ACTH is more effective than cortisone. This may be due in part to the fact that fewer patients have been treated with cortisone. It would seem also that in some instances insufficient amounts of cortisone were administered.

TABLE V
SUMMARY OF RESULTS OF CORTISONE THERAPY IN ULCERATIVE COLITIS

Author	No. of Patients Treated	No. of Patients Benefited
Dearing and Brown, 1950	4	2
Machella and Hollan, 1950	3	2
Kirsner and Palmer, 1951	5	1
McKell et al., 1951	1	1
Milanes et al., 1951	2	2
Redish, 1951	5	0
Gray et al., 1952	5*	3
Total No. of Cases	25	11

* Five episodes in three patients.

TABLE VI
SUMMARY OF RESULTS OF ACTH THERAPY IN ULCERATIVE COLITIS

Author	No. of Patients Treated	No. of Patients Benefited
Dearing and Brown, 1950	1	0
Dutoit and Bauer, 1950	2	2
Randolph, 1950	1	1
Caroll et al., 1951	6	5
Elliott et al., 1951	33	21
Halstead et al., 1951	15	9
Kirsner and Palmer, 1951	40	27
Milanes et al., 1951	5	5
Renold et al., 1951	1	1
Rossmiller et al., 1951	5	1
Gray et al., 1952	8	7
Total No. of Cases	117	79

When improvement occurs in response to either ACTH or cortisone, it usually takes place promptly and is characterized by an increased sense of well being (at times amounting to euphoria), cessation of fever, development of an excellent appetite and gradual subsidence of diarrhea. Erythema nodosum and arthritic manifestations promptly disappear. Roentgen and sigmoidoscopic evidence of improvement

are not observed unless the remission induced has been of sufficient duration, just as is the case when a remission follows any other therapy. Lahey[112] has been so impressed with the ability of ACTH to induce remission in ulcerative colitis that he believes its use has made it unnecessary to perform ileostomy and colectomy during the acute stage when the mortality rate is high.

Not all patients respond to ACTH or cortisone. In the writer's experience, largely confined to use of cortisone, those patients appear to be benefited who are debilitated, those in whom the initial total circulating eosinophils are very low, and those who have associated small intestinal involvement. Patients who are in good general physical condition, those with normal or high eosinophil counts which fail to fall when the compound is administered, and those with insurmountable emotional factors have not, in general, responded. Either compound should not be expected to bring about a cure any more than one expects a cure in arthritis or in any of the other chronic diseases whose manifestations are relieved by the agents. A relapse may occur following discontinuation of treatment if the emotional factors concerned have not been satisfactorily handled during the remission. If the emotional problems have not been solved, the duration of the remission may be prolonged by gradually decreasing the dosage until an effective maintenance level has been reached. If a relapse on the maintenance level occurs, the dosage should be promptly increased.

TABLE VII

SUMMARY OF RESULTS OF MISCELLANEOUS THERAPY

Therapy	No. of Patients Treated	No. of Patients Improved	References to Authors
Adrenal cortex extract	1	1	208
Anti-allergy diet	109	105	5, 179
Arsenic, oral and parenteral	2	2	204
Benadryl	9	5	101
Chlorophyll	11	8	164
Drip, intragastric, colloidal	6	6	146
Enemas, retention of aluminum hydroxide and kaolin	6	6	58
Hyperalimentation (oral)	13	13	125
Hyperalimentation (intravenous)	14	10	152
Ileostomy, medical	13	12	7, 124
Neurectomy, pelvic autonomic	11	10	181
Propylthiouracil	8	8	90, 175
Psychotherapy	48	40	73, 79
Testosterone	7	5	22, 157
Thiouracil*	12	12*	90, 134
Vaccine, autogenous	7	7	88
Vagotomy	74	57	53, 59, 143, 197, 201
Vitamin B_{12}	2	2	165

* Paulley,[175] after a "sufficient" trial with thiouracil, believed that this compound had no advantage over other drugs or no drugs at all.

Psychotherapy. Despite the fact that the importance of psychotherapy has been repeatedly emphasized in the treatment of ulcerative colitis, there are very few series of cases in which psychotherapy alone has been used. (Table VII.) The results from psychotherapy alone are as good as or better than those obtained from many other therapeutic regimens.

The successful management of the emotional aspects of the ulcerative colitis patient calls for a sincere, understanding, helpful and sympathetic attitude not only on the part of the responsible physician but also on the part of all of the personnel who come in contact with the patient. He is frequently hostile and resentful, and tactless words or actions on the part of attendants may impede his progress. Many patients can be handled satisfactorily by the physician acting as his own psychiatrist, particularly if his personality is such that he can instill confidence and arouse hope in a patient who has been subjected to emotional upheavals.

In other instances the aid of a trained psychiatrist may be essential. Whoever attempts to handle the emotional problems concerned must do so tactfully. Unskilled probing into responsible unpleasant motivating mechanisms may at times precipitate an acute fulminating fatal episode or a severe reactive depression which has, on occasion, led to suicide.

Miscellaneous Therapy. The results of treatment of ulcerative colitis with various drugs and therapeutic plans are summarized in Table VII. It will be noted that improvement has attended the use of a wide variety of agents and regimens. One of the reasons for this could very well be their psychotherapeutic value. As stated by Paulley,[150] the simplest form of psychotherapy is reassurance, and this is supplied an ulcerative colitis patient when he sees any doctor who makes an impression on him and in whom he has faith and confidence. If, at the same time, a new remedy is prescribed in a convincing manner the chances are good that the symptoms will remit temporarily.

EXTRACOLONIC DISTURBANCES IN ULCERATIVE COLITIS

The successful management of the ulcerative colitis patient must be individualized not only because of the particular emotional motivating factors concerned but also because of the disturbances which may exist outside the colon. These may be found in the stomach, small intestine, liver, pancreas and kidneys, as well as other organs and tissues of the body.

The appetite may be poor as a result of vitamin deficiency or an associated gastritis, and there may be nausea or vomiting as a consequence of functional gastroduodenal motor disturbances.

The small intestine, as determined roentgenologically by Mackie and Pound,[127] may be the site of changes caused by edema of the mucosa. The normal motor activity may be disorganized and the muscular tone reduced. These authors ascribed the changes to deficiency states as they were most marked and constantly present in those cases showing the most advanced deficiency manifestations. The average small intestinal transport time in thirty-four of their thirty-seven cases for barium was found to be 3.8 (1 to 8) hours. Posey and Bargen[157] also observed deficiency patterns in roentgenograms of the small bowel, as well as hypermotility of the small and large intestine. Cummins[42] has demonstrated marked increases in the motor activity of the small intestine during stress interviews in the ulcerative colitis patients studied by him.

Disturbances in small intestinal absorption may also be present. Elsom et al.[55] regarded the finding of abnormally large excretion of nitrogen in the ileal discharge of four of seven severely ill patients as indicating a defect in the digestive or absorptive function, or both, of the small intestine. The defect disappeared after clinical improvement occurred. More recently Uyeyama et al.[205] found in a group of thirty ulcerative colitis cases a marked reduction in vitamin A absorption, an increased rate of absorption for galactose and a reduced absorption of methionine. Striking and consistent improvement in vitamin A absorption was noted following the administration of ACTH and cortisone.

The small intestine in its entirety, or more frequently in varying lengths of its terminal portion, may be involved by an inflammatory or ulcerative process. The possibility of small intestinal involvement should be kept in mind especially when surgery is contemplated, otherwise the operative result may be unsatisfactory. Ileostomy performed in a diseased terminal ileum frequently means a prolonged convalescence because of fistulas and abscesses. In fact, some surgeons[20] regard the presence of an ileal lesion a contraindication to an operation designed to divert the fecal stream from the colon. Each patient should have his small intestine studied by roentgen means not only as part of the original work-up but also shortly before surgery, if a long interval has elapsed between the original examination and the time when the surgery is to be performed. Evidence of small intestinal involvement may sometimes appear on subsequent examination.

Varying degrees of hepatic insufficiency may occur in ulcerative colitis patients. Comfort et al.[34] described four cases associated with hepatic insufficiency. One of them had evidence of biliary tract disease shortly prior to the onset of the colitis. Tumen et al.[202] reported five cases of hepatic cirrhosis in a total of 151 cases of ulcerative colitis. Four of the five had clinical evidence of cirrhosis. Pollard and Block[154] also described four cases of cirrhosis associated with chronic ulcerative colitis. In two of them the colitis apparently preceded the cirrhosis.

Ross and Swartz[176] analyzed twenty-seven

cases at necropsy for evidence of significant hepatic disease and believed that a definite trend toward hepatic insufficiency existed when weight loss, anemia and activity of the ulcerative disease were marked and that the most significant indicator of such a trend was the finding of a low serum protein level and/or the tendency to reversal of the albumin-globulin ratio. The authors did not find a greater incidence of hepatic insufficiency in ulcerative colitis than was encountered in other diseases in which uncorrected factors of severe anemia, marked weight loss and/or negative nitrogen balance were present. Their analysis of the hepatic function surveys in a series of twenty patients with active disease led them to believe that in no instance did the pattern of liver function tests *per se* justify a diagnosis of latent liver disease. The most frequent findings were excessive urobilinogenuria and a low serum protein value or a tendency to reversal of the albumin-globulin ratio or both. They encountered no chemical or clinical jaundice, no abnormal alkaline phosphatase values and no positive cephalin flocculation tests. The lowest prothrombin level was 56 per cent. Retention of bromsulphalein dye, grades 4, 2 and 1, was observed in three patients. On the other hand, Pollard and Block[154] found that the bromsulphalein and cephalin-cholesterol flocculation tests, prothrombin determination and serum protein values indicated hepatic insufficiency in approximately 50 per cent of their seventy cases. They found histologic evidence of a hepatic pathologic process in eleven of seventeen cases studied postmortem. Degenerative fatty infiltration was most common and definite cirrhosis was present in two instances. The authors believed that hepatic insufficiency in association with ulcerative colitis probably has its origin in fatty changes in the liver which occur as a consequence of severe malnutrition or toxemia or both.

Evidence of interstitial pancreatitis was found by Ball et al.[9] in 53 per cent of eighty-six cases of active chronic ulcerative colitis in which necropsies were performed. The interstitial pancreatitis was acute in two instances and chronic in forty-four. In the latter group the process was severe in five, moderate in seventeen and mild in twenty-two. In addition to the forty-six cases of interstitial pancreatitis there were eleven cases in which definite pancreatic fibrosis and acinar atrophy were present. Pancreatic acinar dilation was found in forty-six cases. The incidence of the lesions was far in excess of those found in a control group of eighty-six cases in which necropsy was performed and ulcerative colitis was not present. Fatty infiltration of the liver commonly accompanied pancreatic disease in the colitis cases. There were no clinical signs of pancreatic disease in the course of the ulcerative colitis.

Evidence of renal tubular degeneration and necrosis was found by Jensen et al.[95] in fourteen of sixty cases of ulcerative colitis which came to necropsy. Calcium deposition was seen in the tubular epithelium of nine specimens. Four of the sixty cases had acute pyelonephritis. The authors, evaluating glomerular function in a group of sixteen patients as measured by urea clearance, found it to be definitely depressed in three patients and questionably depressed in six. The same authors[96] reported a case of amyloidosis associated with chronic ulcerative colitis and referred to two cases in the literature. They suggested that the diagnosis of amyloidosis in the presence of ulcerative colitis be considered in the presence of a persistent, moderate or high degree of albuminuria particularly when associated with a chronic focus of suppuration such as was present in the wall of the colon during repeated exacerbations of the disease in their patient.

A variety of metabolic and other derangements were encountered in forty-four ulcerative colitis cases by Posey and Bargen.[157] The disturbances were proportional to the severity of the disease and included diminished urinary excretion of 17-ketosteroids, abnormal urinary excretion of corticosteroids, impaired adrenal reserve function as indicated by the epinephrine test, steatorrhea, creatorrhea, increased fecal solids, excessive caloric loss in the stools, the development of deficiency states accompanied by deficiency patterns evident in roentgenograms of the small bowel, anemia, diminished values for serum proteins, prothrombin and ascorbic acid, deficiencies of calcium, potassium, sodium and chloride, and metabolic acidosis. The deficiency of potassium was accompanied by typical electrocardiographic alterations. Low levels of serum potassium were also found in four of thirty cases of ulcerative colitis by Lubran and McAllen.[120] A detailed study of one of their cases revealed that the potassium deficiency was due to excessive loss of potassium in the stools. The degree of loss of potassium was closely related to the fluid volume of the feces.

Serum cholinesterase was found to be below normal and the erythrocyte cholinesterase significantly above normal in thirty-five patients with active ulcerative colitis.[142] A return to normal levels for both serum and erythrocyte cholinesterase was demonstrated when ACTH and cortisone were administered as well as when the disease improved without the use of these agents.

PREGNANCY AND ULCERATIVE COLITIS

The questions which may arise regarding the problem of pregnancy and ulcerative colitis are: (1) should the ulcerative colitis patient become pregnant? and (2) once the ulcerative colitis patient has become pregnant or ulcerative colitis has developed during pregnancy, should the pregnancy be terminated? In order to answer these questions information on the effect of pregnancy on the disease and of the disease on the pregnancy is necessary.

An analysis of the reports in the literature[1,60,131,153,203] dealing with the effect of pregnancy on the course of the colitis reveals that in a series of thirty-two pregnancies which occurred during an inactive phase of the disease the colitis was reactivated in 43.7 per cent, while in a group of eighty-eight cases in which pregnancy occurred during an active phase of the disease the colitis improved in 36.3 per cent, became worse in 50 per cent, and was not influenced in 13.6 per cent.

An analysis of reports[1,63,109,153,203] containing data on the effect of ulcerative colitis on the pregnancy reveals that 83 per cent of 136 pregnancies went to full term. The chances of a pregnancy going on to full term therefore are reasonably good when a collected group of patients is considered. One would expect the chances to be still better when a quiescent colitis is not reactivated and in those instances in which the colitis is improved during or by the pregnancy. The observations of Tumen and Cohn[203] and of Abramson et al.[1] clearly indicate that ulcerative colitis developing after the onset of pregnancy may be extremely severe, and that ileostomy may be required to save the patient and permit the pregnancy to go to full term.

It would seem that if the psychosomatic theory of the etiology of idiopathic ulcerative colitis is correct, one would expect the type of results observed. The effect of pregnancy on the disease would depend, as stated by Tumen and Cohn,[203] on the attitude of the patient and of the husband toward the pregnancy. Women who welcome pregnancy do well, while those who do not, do poorly. Palmer[149] also believes that it is not the pregnancy *per se* but the constellation of emotional factors surrounding it which is of importance. Thus the problem of pregnancy or its termination in ulcerative colitis is an individual one. Its solution should be participated in by the responsible physician, the obstetrician and, if necessary, a psychiatrist, and that decision should be made which offers the best prognosis to the patient as well as to the pregnancy.

PROBLEM OF CARCINOMA IN ULCERATIVE COLITIS

The problem of the incidence of colonic carcinoma in ulcerative colitis is a serious one; because if the disease clearly predisposes to an alarmingly high incidence of malignancy, prolonged intensive efforts in medical management should be avoided and surgical extirpation of the colon performed more frequently. A review of the literature up to 1944 by Lynn[121] disclosed a 1.9 (0 to 6.3) per cent incidence of carcinoma in 1,467 cases. A review of the major reports in the literature since 1944 reveals an incidence of 3 (0 to 7) per cent of 6,890 cases. (Table VIII.) The figure of 3 per cent undoubtedly does not represent the true incidence of the complication as this could be obtained only by an examination of the colon of each patient by the pathologist. Furthermore, the figure should be corrected for the natural incidence of carcinoma of the colon, also a difficult figure to obtain.

Figures based on information obtained from surgical and autopsy specimens are generally higher than those based on roentgen and sigmoidoscopic examinations. The point is best illustrated by the report of Kiefer et al.[103] who have two separate series. The incidence of carcinoma in one group of 226 cases (214 of whom had undergone total or partial colectomy and 12 of whom came to autopsy) was 4.4 per cent. In a second group of 458 cases studied by roentgenography and sigmoidoscopy the incidence of carcinoma was 1.9 per cent.

The more frequent occurrence of carcinoma of the colon in ulcerative colitis in an age group younger than in the general population is more impressive than the incidence of carcinoma in ulcerative colitis in general. Sloan et al.[183] found that the mean age at which neoplasm was diagnosed in the Mayo Clinic group of 2,000 cases was forty-two years; and that the greatest

number of neoplastic lesions occurred between the ages of thirty and thirty-nine years. The youngest patient was fifteen years of age at the time of death.

In general the literature is in agreement with regard to the fact that there appears to be a greater tendency for the occurrence of carcinoma in patients who have had the disease a long time. It is also generally agreed that the carcinoma which develops apparently on the basis of ulcerative colitis is usually more malignant than that which arises on the basis of a polyp. Most writers have not been impressed with the tendency of inflammatory pseudopolyps to undergo malignant change.

TABLE VIII

INCIDENCE OF CARCINOMA IN CHRONIC ULCERATIVE COLITIS SINCE 1944

Author	Clinic	No. of Cases	Incidence of Carcinoma	
			No. of Cases	Per cent
Renshaw and Brownell, 1945	Cleveland Clinic (1934–1943)	336	2	0.6
Cave, 1946	Roosevelt Hospital, N.Y.C.	101	4	3.9
Kleckner, 1947	Private Practice, Allentown, Pa.	94	4	4.2
Johnson and Orr, 1948	U. of Kansas Med. Center	164	2	1.2
Ricketts et al., 1948	U. of Chicago	156	3	1.9
Bassler, 1949	Private Practice, N.Y.C.	200	2	1.0
Dennis, 1949	U. of Minnesota Hospital	113	8	7.0
Felsen and Wolarsky, 1949	Bronx Hospital, N.Y.C.	855	0	0
Hayes, 1949	U. of Michigan	451	3	0.7
Lagercrantz, 1949	Karolinska Institute, Stockholm	134	0	0
Logan, 1949	.....	117	1	0.8
Strombeck, 1949	University Hospital	54	1	1.8
Svartz and Ernberg, 1949	Medical Clinic of Carolina Hospital, Stockholm	290	9	3.1
Warren and Sommers, 1949	New England Deaconess Hospital	180	9	5.0
Gleckler and Brown, 1950	Cleveland Clinic (1945–1950)	316	12	3.8
Kapel, 1950	Copenhagen County Hospital	143	2	1.4
Rice-Oxley and Truelove, 1950	Radcliffe Infirmary, Oxford	129	4	3.1
Sloan et al., 1950	Mayo Clinic, Rochester, Minn.	2,000	109	5.4
Brown et al., 1951	Montefiore Hospital, N.Y.C.	147	7	4.8
Kiefer, et al., 1951	Lahey Clinic, Boston, Mass.	684	19	2.9
Lyons and Garlock, 1951	Mt. Sinai Hospital, N.Y.C.	226	9	3.9
Total	.....	6,890	210	3.0

PROBLEM OF TIME OF SURGICAL INTERVENTION IN THE INTRACTABLE CASE

The time at which surgical intervention should be resorted to in the uncomplicated chronic ulcerative colitis patient who does not respond to a good therapeutic regimen frequently represents a serious problem. There are no rigid criteria upon which a decision can be based and each case must be evaluated on an individual basis. Common sense and practical judgment must be exercised. A high mortality of surgery in many instances has led surgeons justifiably to complain that the patient has been permitted to go too long and consequently is a poor risk at the time of operation.

On the other hand, it is highly probable that some patients have been subjected to the risks of surgery and committed to a "life with ileostomy" unnecessarily. Furthermore, anyone with a considerable experience with the disease has seen remission occur, even after months of treatment, often when the situation has appeared to be hopeless.

In intractable cases the writer recommends surgery when he is convinced that the emotional factors motivating the disease are such that they cannot be mitigated or removed for or by the patient and that salvage for economic or other reasons cannot be accomplished otherwise. The possible adverse influence of a perma-

nent ileostomy on the patient's social and economic life are taken into consideration.

SUMMARY

1. The problems presented by certain aspects of chronic idiopathic ulcerative colitis are reviewed. They include those relating to etiology, therapy, extracolonic disturbances, pregnancy, incidence of colonic carcinoma and surgical intervention in the intractable case.

2. The data reviewed do not permit the conclusion that either infection, allergy, deficiency of a specific intestinal factor or excess enzyme production is of etiologic importance. Accumulating experience favors a psychosomatic concept.

3. Analysis of the results of therapy reveals an apparent beneficial response to a wide variety of unrelated agents and regimens in 50 to 100 per cent of the cases.

4. ACTH and cortisone, although not curative, are capable of inducing a remission in some instances. A trial of these agents in adequate dosage is worth while, particularly in critically ill patients when a temporary period of clinical improvement is desired in order to permit sufficient time for the effective use of other therapeutic procedures, especially psychotherapy.

5. The effect of pregnancy on the course of ulcerative colitis has been variable and would appear to depend on the attitude of the patient toward the pregnancy. The clinical course of the disease which develops after the onset of pregnancy is very apt to be extremely severe and drastic measures may be required to save the life of the patient and to produce a viable offspring.

6. A 3 (0 to 7) per cent incidence of colonic carcinoma was found in 6,890 cases of ulcerative colitis collected from the literature.

REFERENCES

1. Abramson, D., Jankelson, I. R. and Milner, L. R. Pregnancy in idiopathic ulcerative colitis. *Am. J. Obst. & Gynec.*, 61: 121, 1951.
2. Almy, T. P. Prolonged clinical remission in ulcerative colitis beginning during pregnancy: a case report. *Gastroenterology*, 17: 450, 1951.
3. Ampler, H. Über die Behandlung der akuten bazillären Dysenterie und schwerer · ulceröser Colitiden. *Wien. med. Wchnschr.*, 96: 297, 1946.
4. Andresen, A. F. R. Gastrointestinal manifestations of food allergy. *M. J. & Rec.*, 122: 271, 1925.
5. Andresen, A. F. R. Ulcerative colitis—an allergic phenomenon. *Am. J. Digest. Dis.*, 9: 91, 1942.
6. Angelo, G. Phthalylsulfathiazole-'sulfathalidine'—a clinical evaluation in 122 patients with proctologic and related conditions. *Am. J. Surg.*, 70: 354, 1945.
7. Anton, A. T. and Secrest, R. Medical ileostomy in ulcerative colitis. *Gastroenterology*, 20: 537, 1952.
8. Baker, W. Y. Psychologic aspects of ulcerative colitis. *Northwest. Med.*, 47: 271, 1947.
9. Ball, W. P., Baggenstoss, A. H. and Bargen, J. A. Pancreatic lesions associated with chronic ulcerative colitis. *Arch. Path.*, 50: 1305, 1950.
10. Banche, M. L'impiego della penicillina in un caso di rettocolite cronica ulcero-purulenta. *Minerva med.*, 2: 512, 1947.
11. Bannick, E. G., Brown, A. E. and Foster, F. P. Therapeutic effectiveness and toxicity of sulfanilamide and several related compounds: further clinical observations. *J. A. M. A.*, 111: 770, 1938.
12. Bargen, J. A. Experimental studies on the etiology of chronic ulcerative colitis. *J. A. M. A.*, 83: 332, 1924.
13. Bargen, J. A. The Modern Management of Colitis. Springfield, Ill., 1943. C. B. Thomas.
14. Bargen, J. A. Sulfathalidine in intestinal disease. *Proc. Staff Meet., Mayo Clin.*, 20: 85, 1945.
15. Bargen, J. A. Evaluation of newer therapy of ulcerative colitis. *South. M. J.*, 41: 646, 1948.
16. Bassler, A. Bacteriology of ulcerative colitis. *M. J. & Rec.*, 138: 472, 1933.
17. Bassler, A. The etiology and treatment of nonspecific chronic ulcerative colitis. *Am. J. Digest. Dis.*, 16: 275, 1949.
18. Bercovitz, Z. T. Chloromycetin therapy of chronic ulcerative colitis: a one year study. *Gastroenterology*, 16: 19, 1950.
19. Block, M. and Pollard, H. M. Chemotherapy and antibiotics in chronic ulcerative colitis. *Gastroenterology*, 10: 46, 1948.
20. Brooke, B. N. and Cooke, W. T. Ulcerative colitis: diagnostic problem and therapeutic warning. *Lancet*, 2: 462, 1951.
21. Brown, A. E., Herrell, W. E. and Bargen, J. A. Neoprontosil (oral) in the treatment of chronic ulcerative colitis. *Ann. Int. Med.*, 13: 700, 1939.
22. Brown, C. H. and Perry, J. H. Medical treatment of acute toxic ulcerative colitis: report of 2 cases. *Cleveland Clin. Quart.*, 16: 126, 1949.
23. Brown, M. L., Kasich, A. M. and Weingarten, B. Complications of ulcerative colitis. *Am. J. Digest. Dis.*, 18: 52, 1951.
24. Brown, P. W. and Bargen, J. A. Bacillary dysentery; late results and relationship to chronic ulcerative colitis. *Am. J. Digest. Dis. & Nutrition*, 5: 562, 1938.
25. Brown, T. R. Chronic ulcerative colitis. *Ann. Clin. Med.*, 4: 425, 1925.
26. Caroll, J. L., Rehfuss, M. E. and Wirts, C. W. The use of ACTH and cortisone in the treatment of idiopathic ulcerative colitis and regional enteritis. Proc. of the 52nd Ann. Meet., Am. Gastroenterological Ass., Atlantic City, June 8, 1951.
27. Cartwright, E. L. Chronic ulcerative colitis. *J. Indiana M. A.*, 31: 66, 1938.

28. Cave, H. W. Late results in the treatment of ulcerative colitis. *Ann. Surg.*, 124: 716, 1946.
29. Cayer, D. and Ruffin, J. M. Treatment of chronic idiopathic ulcerative colitis with sulfaguanidine. *North Carolina M. J.*, 3: 196, 1942.
30. Chewning, C. C. Colitis following oral administration of aureomycin and terramycin. *Virginia M. Monthly*, 79: 136, 1952.
31. Collins, E. N. and Pritchett, C. P. Allergy as a factor in disturbances of the gastro-intestinal tract. *M. Clin. North America*, 22: 297, 1938.
32. Collins, E. N. The treatment of chronic ulcerative colitis with sulfanilamide. *Ann. Int. Med.*, 14: 55, 1940.
33. Collins, E. N. and Hewlett, J. S. Succinyl sulfathiazole (sulfasuxidine) in treatment of chronic ulcerative colitis. *Gastroenterology*, 7: 549, 1946.
34. Comfort, M. W., Bargen, J. A. and Morlock, C. G. The association of chronic ulcerative colitis (colitis gravis) with hepatic insufficiency: report of four cases. *M. Clin. North America*, 22: 1089, 1938.
35. Committee on Therapeutics and Other Agents, National Research Council. *J. A. M. A.*, 132: 4, 1946.
36. Craig, W. M. et al. Report of Penicillin Committee of National Naval Med. Center. *U. S. Nav. M. Bull.*, 44: 473, 1945.
37. Crawford, G. M. and Luikart, R. H. Severe erythema multiforme with intestinal involvement. *J. A. M. A.*, 140: 780, 1949.
38. Crohn, B. B. The clinical use of succinyl sulfathiazole (sulfasuxidine). *Gastroenterology*, 1: 140, 1943.
39. Crohn, B. B. The treatment of non-specific ulcerative colitis. *M. Ann. District of Columbia*, 16: 492, 1947.
40. Crohn, B. B. Discussion. *Gastroenterology*, 15: 282, 1950.
41. Cullinan, E. R. Ulcerative colitis: clinical aspects. *Brit. M. J.*, 2: 1351, 1938.
42. Cummins, A. J. To be published.
43. Dack, G. M., Kirsner, J. B., Dragstedt, L. R. and Johnson, R. A study of B. necrophorum in chronic ulcerative colitis and the effects of sulfanilamide in treatment. *Am. J. Digest. Dis.*, 6: 305, 1939.
44. Daniels, G. E. Treatment of case of ulcerative colitis associated with hysterical depression. *Psychosom. Med.*, 2: 276, 1940.
45. Daniels, G. E. Psychiatric aspects of ulcerative colitis. *New England J. Med.*, 226: 178, 1942.
46. Daniels, G. E. Psychiatric factors in ulcerative colitis. *Gastroenterology*, 10: 59, 1948.
47. Dearing, W. H. and Brown, P. W. Experiences with cortisone and ACTH in chronic ulcerative colitis. *Proc. Staff Meet., Mayo Clin.*, 25: 486, 1950.
48. DeBakey, M. E. and Pulaski, E. J. An analysis of the experience with streptomycin therapy in the United States Army Hospitals. *Surgery*, 20: 749, 1946.
49. Dennis, C. Discussion. *Arch. Surg.*, 58: 249, 1949.
50. Dreiling, D. A. and Richman, A. The pancreas and ulcerative colitis: a case of chronic relapsing pancreatitis complicated by ulcerative colitis. *Gastroenterology*, 17: 568, 1951.
51. Dupuy, R., Parturier, L. M., Berthet, G. and Bauffle, G. H. La peniciline dans le traitment de la recto-colite hemorragique. *Arch. d. mal. l'app. digestif.*, 38: 217, 1949.
52. Dutoit, C. H. and Bauer, W. The effect of ACTH on ulcerative colitis, p. 459. Proc. First Clin. ACTH Conference, Chicago, 1949. Philadelphia, 1950. Blakiston Co.
53. Eddy, F. D. Late results of vagotomy in the treatment of idiopathic ulcerative colitis. *Surgery*, 29: 162, 1951.
54. Elliott, J. M., Kiefer, E. D. and Hurxthal, L. M. ACTH in the treatment of chronic ulcerative colitis. *Gastroenterology*, 19: 722, 1951.
55. Elsom, K. A., Dickey, F. G. and Chornock, F. W. Functional disturbances of the small intestine in chronic idiopathic ulcerative colitis. *Am. J. Digest. Dis.*, 9: 74, 1942.
56. Ehrlick, R. Pathogenesis and treatment of ulcerative colitis with hog stomach. *Am. J. Digest. Dis.*, 14: 294, 1947.
57. Ehrlick, R. Treatment of ulcerative colitis with a fractional component of hog stomach extract. *Am. J. Digest. Dis.*, 17: 1, 1950.
58. Eyerly, J. B. and Breuhaus, H. C. Treatment of ulcerative colitis with aluminum hydroxide and kaolin. *J. A. M. A.*, 109: 191, 1937.
59. Fansler, W. A. and Frykman, H. M. Surgical treatment of non-specific ulcerative colitis. *Am. J. Surg.*, 76: 713, 1948.
60. Feder, J. A. Chronic ulcerative colitis: an analysis of 88 cases. *Am. J. Digest. Dis.*, 5: 239, 1938.
61. Felsen, J. Relationship of bacillary dysentery to distal ileitis, chronic ulcerative colitis and non-specific intestinal granuloma. *Ann. Int. Med.*, 10: 645, 1936.
62. Felsen, J. Bacillary Dysentery, Colitis, and Enteritis. Philadelphia, 1945. W. B. Saunders & Co.
63. Felsen, J. and Wolarsky, W. Chronic ulcerative colitis and pregnancy. *Am. J. Obst. & Gynec.*, 56: 751, 1948.
64. Felsen, J. and Wolarsky, W. Chronic ulcerative colitis and carcinoma. *Arch. Int. Med.*, 84: 293, 1949.
65. Gaither, E. H. Gastrointestinal symptoms of vital significance. *New Orleans M. & S. J.*, 86: 77, 1933.
66. Gill, A. M. Intestinal mucosa in ulcerative colitis. *Lancet*, 2: 202, 1945.
67. Gill, A. M. Treatment of ulcerative colitis with intestinal mucosa. *Proc. Roy. Soc. Med.*, 39: 517, 1946.
68. Ginsberg, R. S. and Ivy, A. C. Etiology of ulcerative colitis. *Gastroenterology*, 7: 67, 1946.
69. Glass, G. B. J., Pugh, B. L., Grace, W. J. and Wolf, S. Observations on the treatment of human gastric and colonic mucus with lysozyme. *J. Clin. Investigation*, 29: 12, 1950.
70. Gleckler, W. J. and Brown, C. H. Carcinoma of the colon complicating chronic ulcerative colitis. *Gastroenterology*, 14: 455, 1950.
71. Grace, W. J., Seton, P. H., Wolf, S. and Wolff, H. G. Variations in concentration of lysozyme with life situations and emotional states. *Am. J. M. Sc.*, 217: 241, 1949.
72. Grace, W. J., Wolf, S. and Wolff, H. G. Life

situations, emotions and chronic ulcerative colitis. *J. A. M. A.*, 142: 1044, 1950.
73. Grace, W. J. and Wolff, H. G. Treatment of ulcerative colitis. *J. A. M. A.*, 146: 981, 1951.
74. Gray, I. and Walzer, M. Studies in mucous membrane hypersensitiveness. III. The allergic reaction of the passively sensitized rectal mucous membrane. *Am. J. Digest. Dis. & Nutrition*, 4: 707, 1937.
75. Gray, I., Horten, M. and Walzer, M. Studies in mucous membrane hypersensitiveness. IV. The allergic reaction in the passively sensitized mucous membranes of the ileum and colon in humans. *Ann. Int. Med.*, 13: 2050, 1940.
76. Gray, I. Discussion. *Am. J. Digest. Dis.*, 9: 97, 1942.
77. Gray, S. J., Reifenstein, R. W., Benson, J. H., Jr. and Young, J. C. G. Treatment of ulcerative colitis with corticotropin (ACTH) and cortisone. *J. A. M. A.*, 148: 1489, 1952.
78. Groen, J. Psychogenesis and psychotherapy of ulcerative colitis. *Psychosom. Med.*, 9: 151, 1947.
79. Groen, J. and Bastiaans, J. Psychotherapy of ulcerative colitis. *Gastroenterology*, 17: 344, 1951.
80. Halstead, J. A., Adams, W. S., Sloan, S., Walters, R. L. and Bassett, S. H. Clinical effects of ACTH in ulcerative colitis. *Gastroenterology*, 19: 698, 1951.
81. Hamilton, J. E., Prandoni, A. G., Evans, J. M. and Romansky, M. J. Penicillin therapy of infections in 220 patients; clinical and bacteriologic study. *Surgery*, 19: 186, 1946.
82. Hardy, T. L. Order and disorder in the large intestine, colon neurosis and ulcerative colitis. *Lancet*, 1: 552, 1945.
83. Hardy, T. E. and Bulmer, E. Ulcerative colitis: survey of 95 cases. *Brit. M. J.*, 2: 812, 1933.
84. Harford, C. G., Martin, S. P., Hageman, P. O. and Wood, W. B., Jr. Treatment of staphylococcic, pneumococcic, gonococcic and other infections with penicillin. *J. A. M. A.*, 127: 253, 1945.
85. Haskell, B. and Friedman, M. H. F. One years treatment of non-specific ulcerative colitis with intestinal extract. *Am. J. Surg.*, 76: 709, 1948.
86. Haskell, B. F. Discussion. *Gastroenterology*, 15: 282, 1950.
87. Hayes, M. A. Chronic ulcerative colitis and associated carcinoma. *Am. J. Surg.*, 77: 363, 1949.
88. Heazlett, W. E. Treatment of chronic ulcerative colitis with staphylococcus autovaccine—a preliminary report. *Gastroenterology*, 10: 634, 1948.
89. Heineken, T. S. and Seneca, H. Phthalylsulfacetamide in ulcerative colitis. *Rev. Gastroenterol.*, 15: 611, 1948.
90. Herfort, R. A. and Livingston, H. H. Thiouracil drugs in the treatment of chronic ulcerative colitis. *New York State J. Med.*, 52: 431, 1952.
91. Hern, J. R. B. Ulcerative colitis. *Guy's Hosp. Rep.*, 81: 322, 1931.
92. Holst, J. E. Chemotherapeutical treatment of severe colitis and proctitis. *Acta med. Scandinav.*, 113: 109, 1943.
93. Hurst, A. F. Ulcerative colitis. *Guy's Hosp. Rep.*, 71: 26, 1921.
94. Hurst, A. F. Ulcerative colitis. *Guy's Hosp. Rep.*, 85: 317, 1935.
95. Jensen, E. J., Baggenstoss, A. H. and Bargen, J. A. Renal lesions associated with chronic ulcerative colitis. *Am. J. M. Sc.*, 219: 281, 1950.
96. Jensen, E. J., Bargen, J. A. and Baggenstoss, A. H. Amyloidosis associated with chronic ulcerative colitis. *Gastroenterology*, 15: 75, 1950.
97. Johnson, T. M. and Orr, T. G. Carcinoma of the colon secondary to chronic ulcerative colitis. *Am. J. Digest. Dis.*, 15: 21, 1948.
98. Jones, C. M. Discussion. *Am. J. Digest. Dis. & Nutrition*, 2: 656, 1935.
99. Kapel, O. Medical and modern surgical treatment of chronic ulcerative colitis. *Acta med. Scandinav.*, 138: 328, 1950.
100. Keefer, C. S., Blake, F. G., Marshall, E. K., Jr., Lockwood, J. S. and Wood, W. B., Jr. Penicillin in the treatment of infections: a report of 500 cases. *J. A. M. A.*, 122: 1217, 1943.
101. Kiefer, E. D. An evaluation of the clinical management of chronic ulcerative colitis. *Gastroenterology*, 10: 16, 1948.
102. Kiefer, E. D. Discussion of Streicher, M. *Gastroenterology*, 15: 282, 1950.
103. Kiefer, E. D., Eytinge, E. J. and Johnson, A. C. Malignant degeneration in chronic ulcerative colitis. *Gastroenterology*, 19: 51, 1951.
104. Kirschner, B. Acute fulminating ulcerative colitis; treatment with streptomycin. *New York State J. Med.*, 46: 525, 1946.
105. Kirsner, J. B., Rodaniche, E. C. and Palmer, W. L. The use of sulfaguanidine in non-specific ulcerative colitis and other infections of the bowel. *Am. J. Digest. Dis.*, 9: 229, 1942.
106. Kirsner, J. B. Discussion. *Gastroenterology*, 15: 282, 1946.
107. Kirsner, J. B. and Palmer, W. L. Effect of corticotropin (ACTH) in chronic ulcerative colitis. *J. A. M. A.*, 147: 541, 1951.
108. Kleckner, M. S. Chronic ulcerative colitis. Proctologic interpretation and treatment. *J. A. M. A.*, 133: 998, 1947.
109. Kleckner, M. S., Jr., Bargen, J. A. and Banner, E. A. Chronic ulcerative colitis and pregnancy. *Am. J. of Obst. & Gynec.*, 62: 1234, 1951.
110. Korostoff, B. B. and King, H. E. Penicillin therapy in ulcerative colitis—a preliminary report. *Am. J. Med. Sc.*, 211: 293, 1946.
111. Lagercrantz, R. Ulcerative colitis in children. *Acta Paediat., suppl.*, 75: 89, 1949.
112. Lahey, F. H. Indications for surgical intervention in ulcerative colitis. *Ann. Surg.*, 133: 726, 1951.
113. Lake, M., Nickel, W. F. and Andrus, W. DeW. Possible role of pancreatic enzymes in the etiology of ulcerative colitis. *Gastroenterology*, 17: 409, 1951.
114. Levine, M. D., Kirsner, J. B. and Klotz, A. P. A new concept of the pathogenesis of ulcerative colitis. *Science*, 114: 552, 1951.
115. Lieberman, W. Streptomycin treatment of intractable ulcerative colitis. *New York State J. Med.*, 46: 2178, 1946.
116. Lindeman, E. Psychiatric problems in conservative treatment of ulcerative colitis. *Arch. Neurol. & Psychiat.*, 53: 322. 1945.
117. Lium, R. Etiology of ulcerative colitis. II. Effect of induced muscular spasm in colonic explants in

dogs, with comment on relation of muscular spasm to ulcerative colitis. *Arch. Int. Med.*, 63: 210, 1939.

118. Lobstein, O. E., Hull, B. J. and Fogelson, S. J. The treatment of gastroduodenal ulcerative disease and ulcerative colitis with detergent complexes. *Gastroenterology*, 20: 474, 1952.
119. Logan, A. H. Chronic ulcerative colitis—a review of 117 cases. *Northwest Med.*, 18: 1, 1949.
120. Lubran, M. and McAllen, P. M. Potassium deficiency in ulcerative colitis. *Quart. J. Med.*, 20: 221, 1951.
121. Lynn, D. H. The relationship of chronic diseases to carcinoma of colon—chronic ulcerative colitis. *Internat. Abstr. Surg.*, 81: 269, 1945.
122. Lyons, C. Penicillin therapy of surgical infections in the U. S. Army. *J. A. M. A.*, 123: 1007, 1943.
123. Lyons, A. S. and Garlock, J. H. Relationship of chronic ulcerative colitis to carcinoma. *Gastroenterology*, 18: 170, 1951.
124. Machella, T. E. and Miller, T. G. Treatment of idiopathic ulcerative colitis by means of a "medical ileostomy" and an orally administered protein hydrolysate-dextri maltose mixture. *Gastroenterology*, 10: 28, 1948.
125. Machella, T. E. Significance of hyperalimentation in treatment of chronic idiopathic ulcerative colitis. *Am. J. M. Sc.*, 7: 191, 1949.
126. Machella, T. E. and Hollan, O. R. The effect of cortisone on the clinical course of chronic regional enteritis and chronic ulcerative colitis. *Tr. Am. Clin. & Climatol. A.*, 62: 67, 1950.
127. Mackie, T. T. and Pound, R. E. Changes in the gastrointestinal tract in deficiency states with special reference to the small intestine. A roentgenologic and clinical study of 40 cases. *J. A. M. A.*, 104: 613, 1935.
128. Mackie, T. T. Discussion. *Am. J. Digest. Dis.*, 9: 97, 1942.
129. Mahoney, V. P., Bockus, H. L., Ingram, M., Hundley, J. W. and Yaskin, J. C. Studies in ulcerative colitis: a study of the personality in relation to ulcerative colitis. *Gastroenterology*, 13: 547, 1948.
130. Major, R. H. The nisulfazole treatment of chronic ulcerative colitis. *Am. J. Med.*, 1: 485, 1946.
131. Maratka, Z. Colitis ulcerosa. *Ceska graficka unie a.s.*, Praha II, Svobodova 1, Czechoslovakia, 1948.
132. Marks, J. A. Wright, L. T. and Strax, S. Treatment of chronic non-specific ulcerative colitis with aureomycin. A preliminary report. *Am. J. Med.*, 7: 180, 1949.
133. Marshall, H. C., Jr., Kirsner, J. B. and Palmer, W. L. The variable effects of sulfonamides on fecal bacteria in patients with chronic ulcerative colitis: a preliminary report. *Gastroenterology*, 14: 418, 1950.
134. Martin, L. Treatment of ulcerative colitis with thiouracil. *Lancet*, 2: 944, 1946.
135. McCready, F. J., Bargen, J. A., Dockerty, M. B. and Waugh, J. M. Involvement of the terminal ileum in chronic ulcerative colitis. *New England J. Med.*, 240: 119, 1949.
136. McKell, T. E., Tuthill, S. W. and Sullivan, A. J. The affective response of a patient with chronic ulcerative colitis to cortisone. *Gastroenterology*, 17: 20, 1951.
137. Meyer, K., Gellhorn, A., Prudden, J. F., Lehman, W. L. and Steinberg, A. Lysozyme in chronic ulcerative colitis. *Proc. Soc. Exper. Biol. & Med.*, 65: 221, 1947.
138. Meyer, K., Gellhorn, A., Prudden, J. F., Lehman, W. L. and Steinberg, A. Lysozyme activity in ulcerative alimentary disease. *Am. J. Med.*, 5: 496, 1948.
139. Meyer, K. and Prudden, J. F. Combined Staff Clinic—Ulcerative colitis. *Am. J. Med.*, 6: 481, 1949.
140. Milanes, F., Spies, T. D., Garcia-Lopez, G., Lopez Toca, R., and Reboredo, A. ACTH and cortisone therapy of chronic ulcerative colitis. Proc. of 52nd. Ann. Meet. American Gastroenterological Assn., Atlantic City, June 8, 1951.
141. Mills, M. A. and Mackie, T. T. The chemotherapy of chronic ulcerative colitis. *Am. J. Digest. Dis.*, 10: 55, 1943.
142. (*a*) Moeller, H. C., Rider, J. A. and Kirsner, J. B : Erythrocyte and serum cholinesterase in ulcerative colitis. *Gastroenterology*, 19: 538, 1951. (*b*) Moeller, H. C., Klotz, A. P. and Kirsner, J. B. Lack of effect of crystalline lysozyme on the isolated intestinal pouch of the dog. *Gastroenterology*, 20: 604, 1952.
143. Moore, F. D. Present status of surgery in ulcerative colitis. *Bull. New England M. Center*, 7: 52, 1945.
144. Morrison, L. M. Results of treatment of ulcerative colitis with salicylazosulfapyridine. *Gastroenterology*, 21: 133, 1952.
145. Murray, C. D. Psychogenic factors in the etiology of ulcerative colitis and bloody diarrhea. *Am. J. M. Sc.*, 180: 239, 1930.
146. Nasio, J. Continuous drip treatment for chronic ulcerative colitis: preliminary report. *Am. J. Digest. Dis.*, 13: 252, 1946.
147. Nickel, W. F., Jr., Gordon, G. M. and Anders, W. DeW. Studies on lysozyme as an etiologic agent in ulcerative colitis. *Gastroenterology*, 17: 406, 1951.
148. Palmer, W. L., Kirsner, J. B. and Marshall, H. Therapeutic considerations in chronic ulcerative colitis. *Ann. Int. Med.*, 32: 627, 1950.
149. Palmer, W. L. Discussion. *Gastroenterology*, 16: 52, 1950.
150. Paulley, J. W. Ulcerative colitis: a study of 175 cases. *Gastroenterology*, 16: 566, 1950.
151. Paulson, M. The present status of idiopathic ulcerative colitis, with special reference to etiology. *J. A. M. A.*, 101: 1687, 1933.
152. Paulson, M. Discussion. *Gastroenterology*, 7: 448, 1946.
153. Patterson, M. and Eytinge, E. J. Chronic ulcerative colitis and pregnancy. *New England J. Med.*, 246: 691, 1952.
154. Pollard, H. M. and Block, M. Association of hepatic insufficiency with chronic ulcerative colitis. *Arch. Int. Med.*, 82: 159, 1948.
155. Portis, S. A., Block, C. L. and Necheles, H. Studies on ulcerative colitis and on some biologi-

cal effects of detergents. *Gastroenterology*, 3: 106, 1944.

156. Portis, S. A. Idiopathic ulcerative colitis. Newer concepts concerning its cause and management. *J. A. M. A.*, 139: 208, 1949.
157. Posey, E. L. and Bargen, J. A. Metabolic derangements in chronic ulcerative colitis. *Gastroenterology*, 16: 39, 1950.
158. (*a*) Poth, E. J. and Ross, C. A. The clinical use of phthalylsulfathiazole. *J. Lab. & Clin. Med.*, 29: 785, 1944. (*b*) Prudden, J. F., Lane, N. and Meyer, K. Lysozyme content of granulation tissue. *Proc. Soc. Exper. Biol. & Med.*, 72: 38, 1949.
159. Prudden, J. F. Treatment of ulcerative colitis with sodium hexadecyl sulfate. *Gastroenterology*, 15: 426, 1950.
160. Prudden, J. F., Lane, N. and Meyer, K. The effect of orally and intra-arterially administered lysozyme on the canine gastrointestinal tract. *Am. J. M. Sc.*, 219: 291, 1950.
161. Prugh, D. G. Variations in attitudes, behavior and feeling-states as exhibited in play of children during modifications of course of ulcerative colitis. *Proc. A. Research Nerv. & Ment. Dis.* (1949), 29: 692, 1950.
162. Prugh, D. G. The influence of emotional factors in the clinical course of ulcerative colitis in children. *Gastroenterology*, 18: 339, 1951.
163. Rafsky, H. A. and Mannheim, P. J. The significance of the Bargen organism as an etiologic factor in ulcerative colitis. *Am. J. M. Sc.*, 183: 252, 1932.
164. Rafsky, H. A. and Krieger, C. I. The treatment of intestinal disease with solutions of water-soluble chlorophyll. A preliminary report. *Rev. Gastroenterol.*, 15: 549, 1948.
165. Rail, G. A. Two cases of ulcerative colitis treated with vitamin B-12. *Lancet*, 2: 816, 1951.
166. Randolph, T. G. Discussion. Proc. First Clinical ACTH Conference, Philadelphia, 1950. Blakiston.
167. Redish, M. H. Failure of cortisone in chronic ulcerative disease of large and small bowel. *Gastroenterology*, 18: 179, 1951.
168. Reifenstein, R. W., Gray, S. J., Connolly, E. P., Spiro, H. M. and Young, J. C. G. Studies on lysozyme in ulcerative colitis. *Gastroenterology*, 16: 687, 1950.
169. Reifenstein, R. W. and Gray, S. J. The effect of adrenocorticotropic hormone upon the fecal lysozyme titre in ulcerative colitis. *Gastroenterology*, 19: 547, 1951.
170. Renold, A. E., Forsham, P. H., Maisterrena, J. and Thorn, G. W. Intravenously administered ACTH: a preliminary report. *New England J. Med.*, 244: 796, 1951.
171. Renshaw, K. J. F. and Brownell, T. S. Carcinoma complicating chronic ulcerative colitis. *Cleveland Clin. Quart.*, 12: 123, 1945.
172. Rice-Oxley, J. M. and Truelove, S. Complications of ulcerative colitis. *Lancet*, 1: 607, 1950.
173. Ricketts, W. E., Kirsner, J. B. and Palmer, W. L. Chronic non-specific ulcerative colitis: a roentgenologic study of its course. *Gastroenterology*, 10: 1, 1948.
174. Rodaniche, E. C., Kirsner, J. B. and Palmer, W. L. The effect of the oral administration of sulfonamide compounds on the fecal flora of patients with non-specific ulcerative colitis. *Gastroenterology*, 1: 133, 1943.
175. Roehlke, A. M. and Tesch, G. Treatment of ulcerative colitis with propylthiouracil. *Minnesota Med.*, 31: 418, 1948.
176. Ross, J. R. and Swartz, J. M. Hepatic dysfunction and cirrhosis in chronic ulcerative colitis. *Gastroenterology*, 10: 81, 1948.
177. Rossmiller, H. R., Brown, C. H. and Ecker, J. A. The effect of ACTH on non-specific ulcerative colitis. *Gastroenterology*, 17: 25, 1951.
178. Rowe, A. H. Chronic ulcerative colitis—allergy in its etiology. *Ann. Int. Med.*, 17: 83, 1942.
179. Rowe, A. H. Chronic ulcerative colitis—an allergic disease. *Ann. Allergy*, 7: 727, 1949.
180. Sammons, H. G. Mucinase in ulcerative colitis. *Lancet*, 2: 239, 1951.
181. Schlitt, R. J., McNally, J. J., Shafiroff, B. G. P. and Hinton, J. W. Pelvic autonomic neurectomy for ulcerative colitis. *Gastroenterology*, 19: 812, 1951.
182. Schlitt, R. J., McNally, J. J. and Hinton, J. W. Response of the distal colon to external stimuli. *Surg., Gynec. & Obst.*, 92: 223, 1951.
183. Sloan, W. P., Bargen, J. A. and Baggenstoss, A. H. Life histories of patients with chronic ulcerative colitis: a review of 2000 cases. *Gastroenterology*, 16: 25, 1950.
184. Snorf, L. D. Chronic ulcerative colitis. *M. Clin. North America*, Chicago No. 35, p. 243, 1951.
185. Spriggs, E. I. Chronic ulceration of colon. *Quart. J. Med.*, 3: 549, 1934.
186. Stewart, W. Ulcerative colitis. *Am. J. Med.*, 6: 486, 1949.
187. Stickney, J. M., Heilman, F. R., Bargen, J. A. and Dearing, W. H. Sulfaguanidine in ulcerative intestinal disease. *Proc. Staff Meet., Mayo Clin.*, 17: 33, 1942.
188. Streicher, M. H. Chronic ulcerative colitis. A clinical summary of the management in 912 cases. *J. A. M. A.*, 118: 431, 1942.
189. Streicher, M. H. Sulfathalidine, clinical evaluation in infectious diseases of the colon. *Illinois M. J.*, 88: 85, 1945.
190. Streicher, M. H. and Pittard, W. Clinical and bacteriological evaluation of oral tyrothricin in chronic ulcerative colitis. Preliminary report. *Proc. Central Soc. Clin. Research*, 19: 1, 1946.
191. Streicher, M. H. Oral administration of penicillin in chronic ulcerative colitis. A clinical, chemical and bacteriologic evaluation. *J. A. M. A.*, 134: 339, 1947.
192. Streicher, M. H., Grossman, M. I. and Ivy, A. C. Preliminary report of a clinical trial of orally administered hog duodenum powder in the treatment of chronic ulcerative colitis. *Gastroenterology*, 12: 37, 1949.
193. Streicher, M. H. Clinical evaluation of orally administered hog duodenal substance in the treatment of chronic ulcerative colitis. *Gastroenterology*, 15: 279, 1950.
194. Strombeck, J. P. The surgical treatment of ulcerative colitis. *Acta chir. Scandinav.*, 98: 414, 1949.

195. Sullivan, A. J. and Chandler, C. A. Ulcerative colitis of psychogenic origin. Report of 6 cases. *Yale J. Biol. & Med.*, 4: 779, 1932.
196. Sullivan, A. J. Psychogenic factors in ulcerative colitis. *Am. J. Digest. Dis.*, 2: 651, 1936.
197. Sullivan, J. M. Surgical treatment of ulcerative colitis. *Wisconsin M. J.*, 49: 773, 1950.
198. Svartz, N. Le traitement des colites ulcereuses par la salazopyrine. *Acta med. Scandinav., suppl.*, 170: 733, 1946.
199. Svartz, N. and Ernberg, T. Cancer coli in cases of colitis ulcerosa. *Acta med. Scandinav.*, 135: 444, 1949.
200. Svartz, N. The pathogenesis and treatment of ulcerative colitis. *Acta med. Scandinav.*, 141: 172, 1951.
201. Thorek, P. Vagotomy for idiopathic ulcerative colitis and regional enteritis. *J. A. M. A.*, 145: 140, 1951.
202. Tumen, H. J., Monaghan, J. F. and Jobb, E. Hepatic cirrhosis as a complication of chronic ulcerative colitis. *Ann. Int. Med.*, 26: 542, 1947.
203. Tumen, H. J. and Cohn, E. M. Pregnancy and ulcerative colitis. *Gastroenterology*, 16: 1, 1950.
204. Udaondo, C. B. Abstract from Archives Argentinas de enfermedades del sparato digestivo y de la nutricion. *J. A. M. A.*, 115: 1034, 1940.
205. Uyeyama, K., Althausen, T. L., Giansiracuso, J. E. and Harper, H. A. Alterations of intestinal absorption in ulcerative colitis and their modifications by "Tween 80," ACTH and cortisone, p. 7. Proc. Am. Gastroenterological Ass., Atlantic City, May 2, 1952.
206. Walzer, M., Gray, I., Strauss, H. W. and Livingston, S. Studies in experimental hypersensitiveness in rhesus monkey: allergic reaction in passively sensitized abdominal organs. (Preliminary report.) *J. Immunol.*, 34: 91, 1938.
207. Warren, S. and Sommers, S. C. Pathogenesis of ulcerative colitis. *Am. J. Path.*, 25: 657, 1949.
208. Webster, J. J. Adrenal cortex in liver disease. *Ann. Int. Med.*, 33: 854, 1950.
209. Wells, J. A., Mercer, T. H., Gray, J. S. and Ivy, A. C. The motor innervation of the colon. *Am. J. Physiol.*, 138: 83, 1942.
210. Wener, J., Hoff, E. H. and Simon, M. A. Production of ulcerative colitis in dogs by the prolonged administration of mecholyl. *Gastroenterology*, 12: 637, 1949.
211. Wener, J. and Polonsky, A. The reaction of the human colon to naturally occurring and experimentally inducted emotional states: observations through a transverse colostomy on a patient with ulcerative colitis. *Gastroenterology*, 15: 84, 1950.
212. White, B. V., Jr. and Jones, C. M. The effect of irritants and drugs affecting autonomic nervous system upon the mucosa of normal rectum and rectosigmoid with especial reference to "mucous colitis." *New England J. Med.*, 218: 791, 1938.
213. Wills, C. B. Use of nisulfazole in treatment of ulcerative colitis. *Rocky Mountain M. J.*, 46: 743, 1949.
214. Wittkower, E. Ulcerative colitis; personality studies. *Brit. M. J.*, 2: 1356, 1938.
215. Wold, L. E. and Baggenstoss, A. H. Gastrointestinal lesions of periarteritis nodosa. *Proc. Staff. Meet., Mayo Clin.*, 24: 28, 1949.
216. Zintel, H. A., Wiley, M., Nichols, A. and Rhoads, J. E. The use of streptomycin in surgical patients. *Surgery*, 21: 175, 1947.

Clinic on Psychosomatic Problems

Hyperventilation in a Patient Who Stammered

Methedrine As an Adjunct to Psychotherapy

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb and Henry H. W. Miles.

DR. ELBERT TUTTLE: The patient is a twenty-four year old housewife who was admitted to the Massachusetts General Hospital five days ago because of attacks of hyperventilation. This symptom first appeared some ten months ago while she was riding in a car with her husband and friends to a party. Since then she has had repeated attacks of rapid breathing that may occur "without reason" during the day at home but are more likely to come on as the patient awakens in the morning or if she goes into crowds, enters subways, buses or taxis. At the onset of an attack there is a great fear of smothering; later a sensation of substernal "tightness" is noted, as well as "tightness" between her temples. If the rapid breathing persists, she experiences paresthesias of her fingers and feels "faint." While the attack may subside spontaneously, relief is more certain if her doctor reassures her, either in person or by telephone.

The patient's parents are of French extraction and they have had little formal schooling. Tuberculosis has caused the death of a number of the parents' siblings. A maternal aunt had a son who stammered. The father is fifty-two years of age, a freight clerk, who eighteen months ago had a serious back injury. Because of this he was retired on a pension. He is described as being more irritable and cross since his injury. His disability made it necessary for his wife to take a job. For this reason the patient and her husband moved into her parents' home thirteen months ago. The mother, aged forty-six, is described as being quiet and hard-working but rather authoritative since becoming the family's main provider. The husband is described as being "happy-go-lucky" and untidy. This untidiness frequently precipitates arguments with the patient's father. Nevertheless the husband is considerate and the patient has felt free to depend upon him as much as upon her mother. Both the patient and her husband express a desire to be able to move back soon to their own apartment and "live their own lives."

The patient is an only child and when she was born her mother's labor was prolonged and difficult. She was bottle fed. Her first memory is of a tonsillectomy at age three, when she was "smothered" by the anesthesia mask. She wet the bed until she was six years old. In the second grade, aged seven, she began to stammer and remembers a fear of being hit on the palms by her teacher, who used this method of punishment on the other students. About the age of eight she saw a movie "The Mark of the Vampire" and ever since has had a great fear of death and of cemeteries. The patient believes herself to have been spoiled by her mother, upon whom she has developed a great dependency. The mother often speaks for her because of her severe stammering.

At the age of twenty-one the patient thought she had leukemia after a friend died of it. For the past three years she has believed that she might have diabetes. Her present symptom of hyperventilation developed almost a year ago; in regard to this she expresses anxiety that there might be some underlying chest disease. She has frequent nightmares concerned with people who are mourning over death, dying or in caskets. She has also dreamed of being chased by white-clad figures or men with knives.

The patient was a good student and was sociable, getting along best with girls. She

started to work at eighteen as a stenographer and was still working in the same kind of job when the present illness began. She had been apprehensive over the possibility of being transferred to another department of the company for which she worked, fearing the problems of adjusting herself, because of the speech impediment, to a new group of girls. The patient was not transferred but her immediate supervisor was. This resulted in anxiety, as the patient felt considerable dependence upon this supervisor who spoke for her in difficult situations much as her mother did at home. She considered the separation a great loss but remained in her job until four months ago when she resigned, finding it impossible to ride the subway because of her fears and the attacks of hyperventilation.

The patient found the subject of sex a difficult one to discuss. As she and her husband had planned to work during the first year of their marriage, they practiced coitus interruptus as a means of contraception. They now are willing to have children but conception has not occurred.

Routine physical examination and laboratory study brought out nothing remarkable. Her behavior on the ward suggests that she is unable to express hostility and seems anxious always to establish a friendly association with others near her. During her attacks the rate of respiration may reach 50 per minute.

PRESENTATION OF THE PATIENT

The patient was a well developed and well nourished young woman of average height. She was neatly dressed. While pleasant and cooperative, she was ill at ease and her speech impediment was quite marked. She seemed happy to be permitted to leave the room.

DISCUSSION

DR. STANLEY COBB: If I had gone on asking her about things, it would have been slow and painful. After she relaxes does she speak more easily than that?

DR. TUTTLE: The stammer varies. Sometimes there is less difficulty.

DR. LEMOYNE WHITE: Her breathing rate was 28 for half a minute in here.

DR. COBB: It was rapid and she had long sighs, mixing up the speech as well. It is hard for her, this combination. It would be of interest to know if she had a certain amount of hyperventilation all the time. We have had experience in the EEG laboratory suggesting that people with a history of hyperventilation will, in a shorter period of voluntary hyperventilation than usual, show abnormal signs in the EEG. Ordinarily it takes three minutes for breakdown to occur. These hyperventilators often begin showing something by the end of the first minute. They do not have an alkalosis that is measurable but it looks as if they had less reserve. We have had her here for about a week and we want to make a therapeutic plan.

DR. VERNON P. WILLIAMS: I had the impression that in spite of, or along with, anxiety and stammering, although she said she was scared to death, she seemed outgoing and pleasant, not shy and inhibited.

DR. TUTTLE: She is outgoing. She has related well to other patients on the ward. She seems to want to be friendly and makes an effort.

DR. WILLIAMS: To make the face-to-face interviewing easier, do you think you might try sodium amytal or pentobarbital?

DR. HERBERT BARRY, JR.: There is a variant of that which I have used, a mixture of 400 to 600 mg. of sodium amytal with 20 to 30 mg. of benzedrine by mouth. The two drugs are supposedly antagonistic but the combination seems to stimulate speech. You can get a wonderful interview.

DR. ELIZABETH R. ZETZEL: I am trying to think of the psychodynamics. She has a very long history of chronic anxiety symptoms, a stammer, inability to stay alone and hypochondriasis. It is important to know how many of these symptoms are linked with hostility. She has fears connected with death; not only of dead people but also of being dead herself. The stammer seems related to ambivalent feelings. Where she feels conflict, her stammer is worse. The origin of the recent acute symptoms can be understood in terms of the events which brought her back into the parents' home and into such a close relationship with her mother. In the first place her old fears and ambivalence had interfered with marital adjustment. At home, ambivalence towards mother increased and led to more difficulty with her marriage relations. On top of that her supervisor was transferred, throwing her back again into the intense relationship with her mother. I would think that these factors had a great deal to do with the onset of the attacks of hyperventilation, which represent an acute form of anxiety. Her fear of aggression is turned back onto herself. She is afraid of being

alone, afraid of closed places. One would guess that her neurosis went back to the traumatic experience of the tonsillectomy. I would not say that the operation was the *cause* because she is a predisposed person. We see in her past history a number of things which contribute to her anxiety: The stress of an early operation and the fact that she is an only child and overprotected. Anxiety-provoking experiences of childhood which ordinarily are not serious made an extreme mark on her. She remembers seeing the movie; remembers seeing the casket taken out. Her experience with these was beyond normal.

In therapy I would work in terms of the recent situation. Find out her feelings about being home, her feelings about change in supervisors. See if one could mobilize the resentful feelings which are just below the surface. I think she should be a good case for therapy but it would be a lengthy process. I would like to see her start as an inpatient and carry on as an outpatient.

Dr. Cobb: She had a lot of work on speech at school and various other places. Was that all speech exercise?

Dr. Tuttle: It was all aimed at the symptom.

Dr. Cobb: That usually exaggerates the symptom unless the person handling the treatment for stammering is able to use a lot of suggestion and make the patient think that the speech trick he is using is very effective. You usually have to help the stammering by treating the neurosis; and then the stammering will take care of itself.

Dr. White: I would much prefer to leave the life-long problems alone and find out more about the onset of this recent illness and of the acute symptoms which have prevented her from working. I would agree that most of the speech impediments are a neurotic way of handling tension and keeping tension back.

Dr. Cobb: We do not have enough evidence about the inheritance in this case. In many cases of stammering there is a genetic factor, with lefthanders in the family and reading defects in some of them. The neurosis is fixed on the vulnerable speech system rather than on some other. An example of that is in my book, "Borderlands of Psychiatry," with a family tree. But there are a lot of stammerers who do not have the family history. Then you have to explain it on dynamics and the fact that normal speech is a highly organized mechanism and is easily disturbed.

Dr. Henry H. Brewster: Did you think this patient had other symptoms focussed around stammering? Also other symptoms such as concern about her heart? Or did you think that all we saw today was characteristic of stammerers?

Dr. Cobb: A speech defect is an annoying and upsetting symptom because it is always interrupting your relationship with people and there is a constant fear you will get stuck. The fear is especially about specific things, when you have to answer in a specific situation. If you ring a doorbell and know that your name will be asked, that is the one thing hardest for you to say. When you let her do the talking, it will ease up. It is the asking and answering that scares her because she knows she has to answer with a certain word. The main thing to work on with her is the fear. I do not know the origin of that. The pediatricians have had experience with fears of smothering in tonsillectomies.

Dr. Henry H. W. Miles: I agree with Drs. Zetzel and White that one ought to begin therapy by working with current material because only as the patient is able to accept her hostility and feel a little more comfortable about expressing it, and as the relationship to the therapist develops, will she be able to remember earliest experiences. The relationship to the therapist, the "corrective emotional experience" that Alexander has emphasized, is the medium which will help her to accept her aggressive impulses. Interpretation of current material may make it possible for the patient then to bring up old things which she has not been able to talk about before.

Dr. White: How would you handle this patient on a short-term basis? These anxiety patients are a long job.

Dr. Zetzel: I would not be optimistic about brief treatment. I think you should start on current situations. It would not be right to start psychotherapy unless you were prepared to follow along with what you brought out. You would have to be prepared to work with her for a good many months.

Dr. White: If one could work through the present situation, her symptoms might improve enough with a good doctor-patient relationship so that she could go back to work.

Dr. Zetzel: Yes. We see here an acute neurosis superimposed upon a chronic one. One might relieve the recent neurosis to some extent without any effect on the other.

Dr. Daniel Dawes: She seems to have pho-

bias along with other troubles. She needs at least six months' treatment.

DR. COBB: We have to admit that she applied for help for her respiration. If we are able to relieve the hyperventilation and then send her out, the rest we should handle by a regimen that we arrange ahead for a year or two. We might try to go after the respiratory symptom. You can be rather simple in your explanation and suggestion, perhaps using some drug to facilitate the interviews. You should use active therapy to relieve the anxiety attacks and send her to the outpatient department and there work on the fears and other aspects.

FURTHER TREATMENT

A diagnosis was made of anxiety neurosis. Long-term psychotherapy was thought to be the treatment of choice. For the present, however, permissive encouragement to elaborate the emotional content of her current attacks was thought advisable.

Interviews were conducted as suggested but the patient seemed unable to give emotionally significant material. Breathing exercises with the use of a paper bag relieved the feeling of weakness and the paresthesias. She continued in a repetitious way to talk of her dependency on her mother but seemed blocked in the expression of real emotion. It was decided to continue therapy on an outpatient basis, and the patient was allowed to go back to her parents' home. She returned to the hospital within thirty-six hours with a severe attack of hyperventilation and was readmitted to the psychiatric ward. The physician who had been assigned to treat her in the outpatient department, Dr. Charles Keuper, now assumed the management of her case.

She told of her parents' and husband's inability to understand her trouble and how it upset her when they said she could do as well at home as in the hospital. She told of being angry at not being able to speak up when she would like to. She looked forward to the time when she and her husband could have their own home. While it was clear that recrudescence of the hyperventilation coincided with her moving back to her parents' home, and that there was a temporal relationship between the attacks and times of emotional conflict, the more specific causes for her tension were not brought out clearly.

Once back in the ward the patient's attacks subsided promptly. To keep the patient from developing too much dependency upon the hospital, it was decided to "wean" her gradually by allowing short home visits. Little was accomplished following two such trials, with the patient still happy to return to the hospital. Interview material remained dull and repetitive, with the stammer as an added impediment. As the patient seemed to avoid discussing certain topics, it was decided to have Dr. Keuper conduct an interview with the use of methedrine® (D-desoxyephedrine hydrochloride).* An intravenous injection of 12.5 mg. was administered within a thirty-second period, and the interview was then conducted in the usual fashion. The patient seemed very comfortable physically and at ease mentally. She expressed a sense of well-being. Where stammering had previously interfered with communication, there was now little speech impediment. Flow of thought and speech could be stimulated with a minimal amount of questioning. She repeatedly told of her wonderful degree of relaxation and euphoria—a state she had never experienced before nor thought possible.

Besides elaborating upon previously discussed subjects she talked freely of her sexual education and experiences. The most pertinent material forthcoming seemed to revolve around her fear of frigidity and inability to become pregnant during the past year. Sexual compatibility had been achieved with her husband during their first year of marriage but since moving to her parents' house she had experienced no sexual gratification. Her lack of interest in sexual intercourse irritated her husband. This had developed since living with her parents, whose bedroom adjoined that of the patient. In her words, "It seemed as if the whole family were constantly standing around watching! I'll be so glad when we can move and be by ourselves again."

Instead of sending her back for another visit to her parents' home we encouraged her husband to prepare their new apartment for her next trial visit from the hospital. When this was finally accomplished, immediate improvement was noted. She was discharged from the hospital and her attacks of hyperventilation gradually diminished during the following two weeks. Also, certain fears no longer plagued her; namely,

* Product of Burroughs Wellcome & Company, New York.

those concerning crowds, being alone, riding in taxis and frigidity.

FOLLOW-UP

Five months have elapsed since the patient's discharge from the hospital and during this time she has maintained the symptomatic improvement. Although mild attacks of hyperventilation continue, they occur only three or four times a week. The attacks never occur when she is in her own apartment but usually when visiting in her parents' home across the street or when she goes farther than one block away from her house.

It is obvious that her phobias are not much improved, nor is the underlying neurosis appreciably affected, but the presenting symptoms have been largely alleviated. She can now live a fairly normal life at home with her husband and she is able to come to the outpatient department regularly for further treatment.

COMMENT

This case was selected to illustrate a number of interrelated points. The first of these is the function of a staff conference as a sort of "advisory board" to help initiate a treatment program. This patient had been in the ward only a few days and little material had been elicited beyond the routine medical and psychiatric history. From the data available the staff members attempted to understand the psychodynamics of the illness and make some guesses at the probable course of events. The purpose was to formulate a plan of treatment which would represent the most advantageous compromise between the needs of the patient and the available therapeutic facilities.

While the treatment of choice in a case like this is intensive psychoanalytically oriented psychotherapy, such a program is not often feasible in a busy general hospital. One can attack the problem in various other ways. Training the patient in voluntary control of the respiratory rate and rebreathing into a paper bag may help considerably in relieving the symptoms of alkalosis due to hyperventilation. The development of a good doctor-patient relationship permits active intervention in the form of suggesting specific changes in the patient's environment. This type of "environmental manipulation" may effect dramatic remissions in acute neurotic symptomatology but one must be careful in evaluating such "improvement" to differentiate between relief of an acute situational conflict and resolution of a more chronic neurosis. Obviously the latter was not accomplished in this case.

With this patient there was difficulty in obtaining free verbalization of certain conflicts and problems of which the patient was fully aware. This was partly due to her marked stammer which interfered with communication and partly to her reluctance and inhibition. It was our impression that the effect of the methedrine was not limited to its pharmacologic properties. The emotional experience was very important, too. The patient felt greatly relieved to talk without impediment and was able to discuss emotionally charged material more easily. It is very likely that this experience was important in the further development of her confidence and trust in the therapist—positive transference—which is such an important factor in the success of brief psychotherapy.

For more detailed reports on the use of methedrine in psychiatric practice, the reader is referred to the papers by Levine et al.[1] and Schein and Goolker.[2]

[1] LEVINE, L., et al. Psychological and physiological effects of intravenous pervitin. *Am. J. Psychiat.*, 105: 429, 1948.

[2] SCHEIN, J. and GOOLKER, P. A preliminary report on the use of D-desoxyephedrine hydrochloride in the study of psychopathology and psychotherapy. *Am. J. Psychiat.*, 107: 850, 1951.

Clinico-pathologic Conference

Aplastic Anemia in a Patient Receiving Chloramphenicol

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, C. M. (No. 204634), was a white married banker forty-four years of age who was admitted to the Barnes Hospital for the first time on December 22, 1951, because of fever and abnormal bleeding. The family and past histories were non-contributory. The patient had been in generally good health until October 2, 1951, at which time he noted the onset of burning on urination, chilly sensations and fever. He consulted a physician in his community and was advised to take sulfisoxizole (gantrisin®). After taking this drug for two days he consulted another physician who prescribed chloramphenicol. The patient's symptoms rapidly abated and he discontinued therapy. Four or five days later, however, because of a recurrence of the same complaints, he resumed chloramphenicol treatment. In the next few weeks he took chloramphenicol whenever urinary symptoms recurred. He finally sought medical care and was referred by a urologist to an outside hospital on November 2nd. There the patient's physical examination was essentially negative except that the prostate was soft and tender. The prostatic secretion contained a large number of white cells. A two-glass urine test showed a large number of white cells in the first specimen but relatively few in the second. The hemoglobin was 15.5 gm., the white cell count 6,200, and the differential count showed 2 per cent eosinophils, 2 per cent band forms, 45 per cent segmented forms, 40 per cent lymphocytes and 11 per cent monocytes. The platelet count was normal, as was the non-protein nitrogen. Intravenous pyelograms were negative except for the presence of two collecting systems on the left side. Cystoscopic examination revealed that the bladder mucosa was normal although there was moderate injection of the trigone. The ureteral orifices were normal but the prostatic urethra was injected. Bladder urine obtained under sterile precautions revealed no bacteria on direct smear; on culture coliform organisms were recovered. The patient was discharged with a diagnosis of prostatitis and advised to continue chloramphenicol. It was also suggested that he see his own physician for prostatic massage and regulation of antibiotic therapy.

The patient consulted his physician only occasionally but continued to take chloramphenicol when he had symptoms. On November 30th he experienced another bout of urinary symptoms and saw his physician, who prescribed a triple sulfonamide preparation which the patient took until December 6th. That morning, while away on a business trip, he noted a skin eruption when he awakened and he had difficulty controlling bleeding from a small cut incurred while shaving. He consulted a physician, who told him to stop the sulfonamide therapy and return home immediately to the care of his own doctor. The latter sent the patient into an outside hospital where he was found to have many petechiae in the skin and mucous membranes. The laboratory data following several blood transfusions, included the following: red blood cell count, 5,530,000; hemoglobin, 17.1 gm.; platelets, 31,000; reticulocytes, 1 per cent; white blood cell count, 1,600; differential count, 96 per cent mature lymphocytes; 4 per cent immature lymphocytes. Bone marrow aspiration showed only a few small bits of marrow, consisting mainly of amorphous material and fat globules. Very few cells were seen. The differential count was recorded as follows: 1 "C" myelocyte, 1 "B" myelocyte, 2

reticulum cells, 2 phagocytic clasmatocytes, 82 lymphocytes, 12 plasma cells and 2 normoblasts per 100 white blood cells.

During the patient's hospital stay gross hematuria, multiple ulcers on the buccal mucosa and epistaxes developed. Penicillin and streptomycin therapy were given initially, but after several days streptomycin was discontinued and chloramphenicol reinstituted. The patient was seen in consultation by a member of the Hematology Division of this Department who called attention to the possible relationship between chloramphenicol and aplastic anemia. He advised that the drug be stopped. While in the hospital the patient received a total of eight blood transfusions, the last of which was followed by a severe febrile reaction. In the hope that febrile transfusion reactions of this type could be avoided the patient was transferred to the Barnes Hospital on December 22nd for further care.

At the time of entry physical examination revealed the temperature to be 38.5°C., pulse 34, respirations 20 and blood pressure 120/80. The patient was a well developed, well nourished male who appeared acutely ill. Numerous purpuric and ecchymotic areas were noted in the skin and mucous membranes. There were multiple necrotic ulcers in the buccal mucosa and several smaller ulcers were seen on the tongue. Some of the ecchymotic lesions over the skin of the back were secondarily infected as evidenced by the presence of small abscesses in these sites. There was no lymph node enlargement. The lungs were clear to percussion and auscultation. Examination of the heart was negative. Examination of the abdomen revealed no palpable masses or organs and no tenderness. The remainder of the physical examination was within normal limits.

The laboratory data were as follows: red blood cell count, 4,710,000; hemoglobin, 14.7 gm.; white blood cell count, 2,000; differential count, 95 per cent mature lymphocytes; 5 per cent young lymphocytes. No platelets were seen on the slide of the peripheral blood; the red blood cells appeared normal. Urinalysis: specific gravity, 1.019; albumin, 4+; sugar, negative; sediment, innumerable red blood cells. Stool guaiac was strongly positive. Cardiolipin test: negative. Bleeding time: greater than twenty-five minutes. Clotting time (Lee-White method): fifteen minutes. Clot retraction: none at twenty-four or forty-eight hours. Blood cultures: negative. Blood chemistry: non-protein nitrogen, 39 mg. per cent; sodium bilirubinate, 0.62 mg. per cent; bilirubinglobin, 1.39 mg. per cent; cephalin-cholesterol flocculation test, 2+; thymol turbidity test, 1 unit; total proteins, 4.2 gm. per cent; albumin, 2.4 gm. per cent; globulin, 1.8 gm. per cent.

During the patient's stay in the Barnes Hospital many blood counts were done. The red blood cell count varied from a maximum of 4,710,000 to a minimum of 1,940,000. The hemoglobin ranged from 14.7 to 6.4 gm. There was a constant neutropenia, the white blood cell counts being between 750 and 1,600. The platelet count was often 0 and never above 31,000, and the reticulocytes were never above 1 per cent. Differential counts showed that the majority of cells were always mature lymphocytes. On several occasions, however, numerous cells having the characteristics of plasma cells were observed, and on one count 6 normoblasts per 100 white blood cells were seen. Bone marrow examination was not repeated.

The patient's course was one of progressive deterioration. He bled profusely from the gastrointestinal tract and from the nasopharynx, so that one of the most difficult problems facing those taking care of him was the maintenance of his erythrocyte and hemoglobin levels. Several severe transfusion reactions of a febrile nature occurred. They were partially prevented by using only donor blood which gave a negative indirect Coombs test, and by administering benadryl® at the time of each transfusion. The patient's temperature remained elevated throughout his hospital stay and in the last few days of life was above 40°C. He received as many as 12 units of whole blood in a twenty-four-hour period. At times twitching of the muscles of the face and body was noted and was relieved by the administration of intravenous calcium gluconate. The serum calcium was 7.2 mg. per cent and the phosphorus 2.1 mg. per cent. Other therapy included parenteral vitamins and analgesics. Penicillin, terramycin and streptomycin were also given. Intravenous protamine did not benefit the bleeding tendency, nor did cortisone given in a dose of 200 mg. daily. In the last twenty-four hours of life the patient's pulse became weaker and the rate gradually increased to 140 per minute. His respirations rose to 50 per minute and he became cold and clammy. He lapsed into coma and expired quietly on December 29th. During the seven

days he was in the Barnes Hospital he had received thirty-eight blood transfusions.

CLINICAL DISCUSSION

DR. CARL V. MOORE: The patient's present illness, which is reviewed in detail in the protocol, makes it clear that he had had repeated exposure to chloramphenicol. In addition, he took sulfonamide drugs on more than one occasion. For a period of several months during which he took chemotherapeutic drugs for urinary tract symptoms he apparently exhibited no untoward effects attributable to drug sensitivity. Suddenly, then, profound bone marrow aplasia developed and despite all supportive therapy he succumbed in about three weeks. I believe it would be well to begin our discussion by considering the problem which led this patient to seek medical care originally and for which the antibiotic therapy was prescribed, namely, the urinary tract symptoms. I should like to inquire if Dr. Cordonnier believes prostatitis alone could have explained the urinary tract symptoms.

DR. JUSTIN J. CORDONNIER: In general it would be unusual for prostatitis to be as persistent as apparently was the case here. One must take into consideration, however, the fact that the patient depended on "self-medication" a good bit of the time, treating his symptoms without benefit of knowledge of the state of the disease itself. Although I did not see this man originally, I know that the urologist who studied his case is an extremely competent person. Therefore, I would accept without question the fact that there was no other abnormality of the genitourinary system and attribute the patient's symptoms to prostatitis, inadequately treated.

DR. C. V. MOORE: Would you comment on the diagnosis of prostatitis?

DR. CORDONNIER: The diagnosis of acute prostatitis is usually rather obvious for the gland is enlarged and tender, and the patient exhibits the typical signs of acute bacterial infection. By contrast, the diagnosis of chronic prostatitis may be more difficult. In either case the prostatic secretion should be examined microscopically; and if numerous white blood cells are not present, the diagnosis of prostatitis should be questioned. Cultures are often unsatisfactory because of the contamination of prostatic secretion in the urethra.

DR. C. V. MOORE: What is the treatment of choice for prostatitis?

DR. CORDONNIER: That is a difficult question, Dr. Moore. Management of the disease has changed considerably in the past fifteen years because of the advent of chemotherapeutic agents. In office practice—and most patients with prostatitis are ambulatory—parenteral administration once or twice weekly of penicillin and streptomycin, supplemented by daily oral sulfadiazine or sulfisoxizole, is an effective method. Prostatic massage twice weekly is an important adjunct to therapy. Frequent microscopic examination and culture of prostatic secretion is important in gauging the therapeutic response. If the causative organism can be isolated, its sensitivity to the antibiotics can be determined.

It is important to point out that disappearance of symptoms alone is not sufficient indication for cessation of drug treatment, although a significant number of patients unfortunately do what this man did, i.e., discontinues treatment as soon as the symptoms abate.

We have, of course, also used aureomycin, chloramphenicol and terramycin in the treatment of prostatitis. In our experience aureomycin or terramycin has been more effective usually than chloramphenicol. With aureomycin the occurrence of nausea and diarrhea has in some instances made it necessary to switch to another agent.

DR. THOMAS H. HUNTER: What organisms are most often recovered, Dr. Cordonnier, from the prostatic secretion? I am aware of the difficulties, to which you have already alluded, involved in attempting to culture this particular secretion.

DR. CORDONNIER: Coliform organisms are recovered most frequently. Staphylococci and streptococci are also found with some degree of frequency. The widespread use of antibiotics has influenced the nature of the infecting organisms in that as susceptible bacteria are killed, resistant ones, such as those of the aerogenes group and Bacillus proteus, may emerge.

DR. C. V. MOORE: Dr. Hunter, do you have any additional comments to make concerning the antibiotics?

DR. HUNTER: I have had practically no experience in the treatment of prostatitis, Dr. Moore. As Dr. Cordonnier has pointed out, the choice of a drug is a problem because of the difficulty of obtaining bacteriologic data upon which to base the choice. For this reason one of the broad-coverage antibiotics should be es-

pecially useful, and I would lean toward aureomycin or terramycin. Most of us in the Department of Medicine are conservative in the use of sulfonamides because of our occasional alarming experience with them in terms of serious reactions of hypersensitiveness.

DR. CORDONNIER: I agree that broad spectrum coverage is desirable but in our hands the combination of penicillin, streptomycin and a sulfonamide has been extremely effective.

DR. HUNTER: Can't one make a case for abandoning the sulfonamides? Will they do anything that terramycin or aureomycin will not? I take this stand, as I have said, because of the occasional serious toxicity associated with sulfonamide therapy.

DR. CORDONNIER: I fully realize that there is a hazard involved in the use of the sulfonamides, but as I have already mentioned, the unpleasant gastrointestinal manifestations attributable to aureomycin can limit its effectiveness. Although terramycin has often satisfactorily combatted the prostatic infection, we have seen intractable proctitis on more than one occasion when this drug was used. For this reason, I tend in general to obtain wide spectrum coverage with another agent or combination of agents.

DR. HARRY L. ALEXANDER: What dose of sulfonamide do you prescribe?

DR. CORDONNIER: We use either 1 gm. of sulfadiazine four times a day or 2 gm. of sulfisoxizole four times a day.

DR. ALEXANDER: Do you ever combine the two?

DR. CORDONNIER: No, we use one or the other.

DR. ALEXANDER: It seems to me that this dosage is a small one and it interests me that you find it effective.

DR. CORDONNIER: In our experience doses of this order have been adequate.

DR. C. V. MOORE: I would like to turn the discussion now to another problem which is of extreme interest and importance, namely, the aplastic anemia. First of all, Dr. Loeb, do you believe that there are sufficient data to accept the diagnosis of aplastic anemia without question? If you do, would you explain the appearance of plasma cells and nucleated red cells in this man's peripheral blood.

DR. VIRGIL LOEB, JR.: The hematologic abnormality, which was present for only a relatively short time during this patient's illness, was characterized by thrombocytopenia, leukopenia and absolute granulocytopenia. In addition, he also exhibited reticulocytopenia. These findings, I think, add up to one of two diagnoses, either acute aplastic anemia or acute leukemia. When they are coupled with evidence of a hypocellular bone marrow, the absence of an abnormal cell type, either in the bone marrow or the peripheral blood, and the absence of peripheral lymph node enlargement or splenomegaly, the diagnosis of acute aplastic anemia can be applied without much reservation. Your second question in regard to the presence of nucleated red cells and plasma cells in the blood during the terminal illness is more difficult to explain. One explanation, a relatively easy one, is merely to state that when any individual has a white blood cell count of 800 to 1,000, a differential count is inaccurate. Thus relatively few plasma cells may indicate a relatively high percentage, when in terms of absolute numbers they are not present in an abnormal quantity. Mention should also be made of the fact that the patient received cortisone during his hospitalization here. Cortisone does have some myelostimulatory effect, and it is possible that some resting focus of red cell production was stimulated, with the result that normoblasts appeared in the peripheral blood. Certainly there were very few of them. Finally, in the agonal state, for reasons unknown to me, one occasionally finds cells in the peripheral blood which normally remain in the marrow.

DR. C. V. MOORE: Do you have any additional comments, Dr. Reinhard?

DR. EDWARD H. REINHARD: I should like to ask a question first. It is my impression that this patient did not have plasma cells in his blood when first seen and that the plasma cells appeared only during the terminal course. Is that correct?

DR. C. V. MOORE: Yes, it is.

DR. REINHARD: In that case I would suggest that this patient was suffering from a granulomatous disease which was responsible for the plasma cell response; plasma cells are commonly associated with a number of granulomas. In favor of this hypothesis is the fact that this patient had received a remarkable amount of chemotherapy of various types during his illness, and it is therefore conceivable that terminally he was suffering from a fungus infection which arose because of the suppressive effects of the various antibiotics on the normal body flora. Such an infection could have produced a plasma cell response.

DR. C. V. MOORE: That is certainly a tenable explanation and we shall return to it later. All of us here are aware of the interest in the possible relationship between chloramphenicol and bone marrow aplasia. It is important to point out that many of the patients in whom aplastic anemia developed while receiving chloramphenicol have also been taking other antibiotics. Such is the case with this patient whom you will recall received sulfisoxizole, a triple sulfonamide, streptomycin and penicillin. Dr. Harrington, will you review the evidence regarding the relationship of chloramphenicol to aplastic anemia.

DR. WILLIAM J. HARRINGTON: To date 129 cases of aplastic anemia, which have occurred in patients receiving chloramphenicol, with or without other antibiotics, have been reported. Approximately one-half of the patients were receiving additional drugs. It has been estimated that eight million patients have been treated with chloramphenicol since its introduction. Employing these two figures one can calculate that the incidence of this blood dyscrasia is of the order of 1 in 800,000. Assuming that the incidence was even twice as large, it is clear that it would still be so small as to render it very difficult to study the problem experimentally. One must, by necessity, be conjectural at this time. The most impressive evidence incriminating the antibiotic as an etiologic factor, I believe, is that aplastic anemia developed in about twenty-three patients while receiving chloramphenicol alone; none of these patients had evidence of a concomitant disease characterized *per se* by marrow hypoplasia. The etiologic relationship of drugs to blood dyscrasias is an old and difficult one, especially when the incidence of the given toxic manifestation is low. Aminopyrine affords an example in which the relationship of a particular drug to a blood dyscrasia was fairly well confirmed. In Denmark some years ago the incidence of agranulocytosis in patients receiving aminopyrine was relatively high, being estimated at 1 per 100,000 patients. When the administration of aminopyrine was stopped throughout the country, the incidence of agranulocytosis declined to essentially zero. Recently Moeschlin[1] has presented evidence indicating that the phenomenon of agranulocytosis after aminopyrine therapy may represent an adverse antigen-antibody reaction. Previously, Kracke and Parker,[2] Madison and Squier,[3] and Dameshek[4] showed that the development of agranulocytosis in patients given aminopyrine involved their being sensitive to the drug, an observation probably predictable from the relatively small incidence of untoward reactions. The tendency of this drug to produce hypersensitiveness was attributed to the presence of a benzamine group. It is of interest in this regard that Smadel,[5] in 1949, pointed out that chloramphenicol, which contains a nitrobenzene ring, might eventually produce some blood dyscrasia. In 1950 there were three separate reports of hematologic abnormalities occurring in patients receiving chloramphenicol. Subsequently, as I have indicated, the number of reports has risen steadily. It therefore seems quite likely that in certain instances chloramphenicol causes aplastic anemia, but the incidence of this dyscrasia is extremely low in terms of the number of patients who have received the antibiotic. Nonetheless, the calculated risk must be borne in mind when it is administered.

DR. C. V. MOORE: Dr. Reinhard, do you have anything to add to what Dr. Harrington has said? Would you comment particularly on the duration of treatment and the total dose of chloramphenicol used as each relates to the development of aplastic anemia.

DR. REINHARD: Most of the patients give a history of having had chloramphenicol previously on one or more occasions. A smaller number, who have received only a single course of chloramphenicol over a long period of time, late in the course of therapy or even after its cessation, have developed aplastic anemia. It is important to emphasize the fact that in a number of patients the first manifestation of aplastic anemia appeared several months after treatment was discontinued. As a first approxi-

[1] MOESCHLIN, S. and WAGNER, K. Agranulocytosis due to the occurrence of leukocyte-agglutinins (pyramidon and cold agglutinins). *Acta haemat.*, 8: 29, 1952.

[2] KRACKE, R. R. and PARKER, F. P. The etiology of granulocytopenia (agranulocytosis). *J. Lab. & Clin. Med.*, 19: 799, 1934.

[3] MADISON, F. A. and SQUIER. T. L. Etiology of primary granulocytopenia (agranulocytic angina). *J. A. M. A.*, 102: 755, 1934.

[4] DAMESHEK, W. and COLMES, A. The effect of drugs in the production of agranulocytosis with particular reference to amidopyrine sensitivity. *J. Clin. Investigation*, 15: 85, 1936.

[5] SMADEL, J. E. Chloramphenicol (chloromycetin) in the treatment of infectious diseases. *Am. J. Med.*, 7: 671, 1949.

mation, therefore, aplastic anemia is apt to occur in patients who have taken chloramphenicol for a considerable period of time or who have been exposed to it on repeated occasions. There are a few exceptions to this statement but not very many.

DR. C. V. MOORE: Should any of the other drugs which this patient took be considered as a possible factor in causation of the blood dyscrasia?

DR. REINHARD: Two of them merit attention in this regard. The sulfonamides most frequently have been implicated in the production of agranulocytosis as a hematologic disorder, but rarely aplastic anemia has been reported after sulfonamide therapy. It is doubtful that the sulfonamides were important in this case, but one cannot rule out that possibility completely. Streptomycin also has been implicated in the production of aplastic anemia, but as far as I know only in one report, that of Deyke and Wallace[6] in 1948. They studied 400 tuberculous patients in the Fitzsimmons General Hospital treated over a long period of time with streptomycin. Aplastic anemia developed in two patients in this group of 400, in one on the seventy-ninth day and in the other on the ninety-fifth day of treatment. One of the patients had received no other medication except secobarbital (seconal), and the other had received, in addition to streptomycin, only diphenhydramine (benadryl). It was concluded that neither of these drugs was responsible, and that streptomycin had caused aplastic anemia in these two instances. I know of no others.

DR. ALBERT I. MENDELOFF: In the Proceedings of the National Meeting of the American Federation for Clinical Research[7] there is a report concerning the effect of chloramphenicol on erythropoiesis. In three of eight patients erythropoiesis was depressed during a thirty-day course of the drug. When chloramphenicol was withdrawn, the hematologic findings returned to normal. A second exposure to chloramphenicol resulted in erythropoietic depression in two of the three patients; as before, the red blood counts returned to normal after cessation of antibiotic therapy.

[6] DEYKE, V. F. and WALLACE, J. B. Development of aplastic anemia during the use of streptomycin. *J. A. M. A.*, 136: 1098, 1948.

[7] LINDAU, W. Effect of Chloromycetin upon Erythropoesis, Abstract #72 in: The Proceedings of the National Meeting of the American Federation for Clinical Research, 1952.

DR. C. V. MOORE: It is of interest in discussing this problem to recall that about eighteen months to two years ago synthetic chloramphenicol became available; previously, the fermentation product was used. It is estimated that only 10 to 15 per cent of the chloramphenicol now available comes from the fermentation process and the rest is synthetic. It is important, therefore, to know if some toxic substance has contaminated the synthesized material and has been responsible for the dyscrasias reported. There is no answer to this question at present. Before concluding our discussion of the cause of aplastic anemia in this patient, we must mention the possibility that idiopathic aplastic anemia had developed coincidentally. This explanation can neither be substantiated nor refuted with certainty, although it is probably unlikely. In summary it can only be said that this case presents another instance in which aplastic anemia developed in a patient while he was receiving chloramphenicol; to date there is no way in which one can assign unequivocally the cause of the dyscrasia to this antibiotic. The relationship of chloramphenicol to aplastic anemia could be more conclusively demonstrated if a patient who had developed aplastic anemia while on the drug and then recovered were subsequently given the drug again and developed a recurrence. No investigator would knowingly perform this experiment.

To date about 50 per cent of the patients in whom aplastic anemia developed while receiving chloramphenicol have recovered. This patient received many transfusions, vigorous efforts were made to control secondary infection and he was given cortisone. These measures failed to save this man's life. Dr. Chernoff, would you comment on the role of therapy in regard to the chance of recovery. Are there any other therapeutic measures which should be used, or are those which were employed here the only ones indicated?

DR. AMOZ I. CHERNOFF: The situation encountered here is comparable to that which obtains when agranulocytosis is produced by drug idiosyncrasy. Treatment is designed to tide the patient over the critical period until bone marrow recovery takes place. In the presence of anemia transfusions should be given and the use of other antibiotics to prevent secondary infection is definitely indicated. Whether cortisone and ACTH have a place in therapy is open to question, especially since the recent report by

Thiersch et al.[8] in which it was shown that in one type of marrow depression—that due to irradiation—cortisone exhibited a detrimental effect.

DR. C. V. MOORE: Whether chloramphenicol should continue to be used or whether it should be withdrawn from the market was considered recently by the Food and Drug Administration which asked an *ad hoc* committee of the National Research Council to make a recommendation in this regard. The recommendation, which has been accepted, stated that chloramphenicol was too effective an agent to be removed from the market, even if it was accepted that it was responsible for the cases of aplastic anemia reported. It is being marketed, therefore, with a warning on the label that it can cause hematologic abnormalities and that it should not be used for minor infections. Dr. Hunter, what do you consider the indications for chloramphenicol?

DR. HUNTER: First of all, I agree that it should not be withdrawn from the market, even if one does accept its role in the production of aplastic anemia. In the treatment of human disease we are forced to use a number of agents which entail a distinct hazard, and part of one's medical education is to learn to evaluate the relative risks which are at stake. On this basis I believe there are still definite indications for chloramphenicol. Before discussing the indications for the drug I would like to emphasize the fact that there are a number of situations in which it should not be employed. The practice of using chloramphenicol to treat respiratory infections which can be controlled adequately with one or another agent is to be avoided. Similarly, chloramphenicol should not be given patients with urinary tract infections if aureomycin, terramycin or streptomycin can be employed instead. Obviously the prolonged use of chloramphenicol is unwise since, as Dr. Reinhard has pointed out, there seems to be a distinct correlation between the length and multiplicity of courses of chloramphenicol and the incidence of blood dyscrasias. Where then should it be used? In my opinion there is no agent now available which is as satisfactory in the treatment of patients with typhoid fever; since typhoid fever is a serious disease, the use of chloramphenicol is justified. The risk is minimal at most if the drug is given for ten days or two weeks to patients suffering from typhoid fever. Further, chloramphenicol may be the most effective agent against the proteus group, so that patients with serious infections due to this organism may justifiably be given it. It should be pointed out that drug sensitivity among proteus strains is variable, and chloramphenicol should be employed only after laboratory evidence indicates that it will afford the most effective means of treatment. There are still a few staphylococal infections which seem to respond to a combination of chloramphenicol and other antibiotics, and recently a case of bacterial endocarditis cured by a combination of penicillin and chloramphenicol has been reported.[9] In the latter case other agents seemed totally ineffective, but it was noted *in vitro* that the combination of chloramphenicol and penicillin was highly bactericidal for the particular strain causing the disease. In summary then, I believe there still is a place for chloramphenicol in the treatment of serious infections, particularly those which endanger life, and where it has been established that chloramphenicol is the most useful of the drugs available.

DR. C. V. MOORE: May we go on now to the last problem and inquire why this patient died; that is, why the transfusions and the other measures employed failed to sustain his life until the bone marrow recovered spontaneously. Dr. Taussig, this question is a difficult one. The patient had a very high fever and was bleeding from all orifices. Although hemorrhage was a most serious problem, I doubt that he died from blood loss. Do you have any comments to make?

DR. BARRETT L. TAUSSIG: I do not know why the patient died, Dr. Moore. As a matter of fact, the immediate cause of death in patients with blood dyscrasias or malignancy is occasionally obscure. I think it very likely in the present case that an overwhelming infection, which was not controlled by the antibiotics, was responsible for the fatal outcome. On the other hand I am sure that some patients with aplastic anemia die even though they do not suffer secondary infection.

DR. C. V. MOORE: That does happen, although in most instances an intracranial hemorrhage or some other obvious explanation

[8] THIERSCH; J. B., CONROY, L., STEVENS, A. R., JR. and FINCH, C. A. Adverse effect of cortisone on marrow regeneration following irradiation. *J. Lab. & Clin. Med.*, 40: 174, 1952.

[9] AHERN, J. J. and KIRBY, W. M. M. Successful cure of subacute bacterial endocarditis with penicillin and chloramphenicol. *J. A. M. A.*, 150: 33, 1952.

can be found. You mention the possibility of severe overwhelming infection and Dr. Reinhard has already suggested a mycotic infection. Do you want to make any additional comment, Dr. Reinhard?

DR. REINHARD: As I indicated earlier the presence of plasma cells in the blood is a finding compatible with an infection of the granulomatous type; and since this patient had prolonged therapy with many antibiotics, the pattern of the indigenous flora in the body cavities may have been altered, resulting in overgrowth by fungi which are normally suppressed.

May I make one other point? A very interesting statement appeared in a recent article by Claudon and Holbrook[10] in the Journal of the American Medical Association. I would like to read it for the purpose of disagreeing with it. They say, "In our opinion careful evaluation should be made of the hematological status of candidates for chloramphenicol therapy, and the drug should not be prescribed when leukopenia or marrow hypoplasia is present. Patients receiving chloramphenicol therapy should be followed with bi-weekly blood counts so that early signs of marrow injury may be discovered. . . ." If one recalls the article cited by Dr. Mendeloff earlier in the discussion, he will remember that there were changes in the blood counts and bone marrow findings in several patients receiving chloramphenicol therapy, but aplastic anemia developed in none of these patients, even on subsequent exposure to the drug. This mild depression is comparable to the well recognized mild leukopenia which occurred in many patients receiving prolonged sulfonamide therapy. The evidence is overwhelming that the leukopenia was unrelated to the occasional development of agranulocytosis in other patients. In other words mild depression of the white or red blood cell count, which may be seen with a number of drugs, is almost certainly an entirely different phenomenon, from the standpoint of pathogenesis, from the explosive onset of a life-threatening blood dyscrasia like agranulocytosis or aplastic anemia which occurs in a very small number of patients. In my opinion, therefore, there is no real evidence to substantiate the implied concept that if one discontinues treatment of patients when leukopenia occurs, the incidence of serious blood dyscrasias will be decreased. Certainly we never hesitated to treat patients with the sulfonamides when they exhibited a leukopenia, and I doubt that bi-weekly blood counts *per se* would be of any real value. A patient can have a normal blood count at nine o'clock in the morning and have the full-blown picture of aplastic anemia six hours later. It is probably impractical to attempt to avoid blood dyscrasias by blood counts or bone marrow examinations.

DR. HUNTER: Further, as you pointed out, some of the dyscrasias do not develop until a significant period after the drug has been withdrawn.

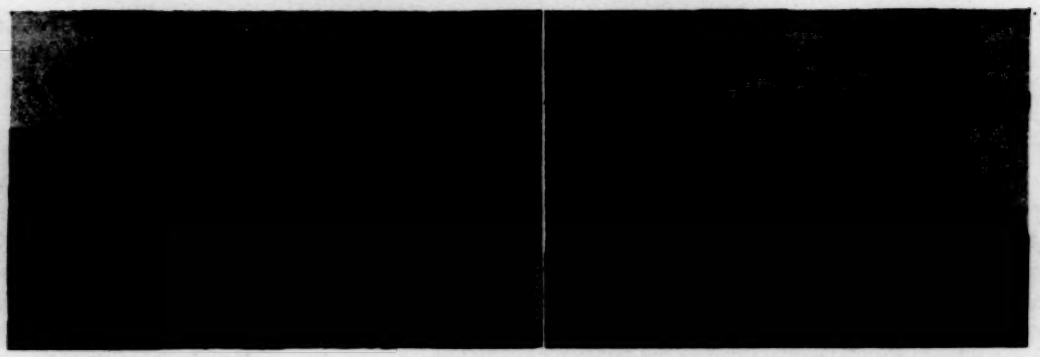
DR. C. V. MOORE: I think Dr. Reinhard's point is certainly an important one which must be emphasized. In summarizing this discussion I believe the consensus certainly favors the diagnosis of aplastic anemia in this patient, and it is suspected that chloramphenicol may have caused the dyscrasia. The patient probably had prostatitis but no other specific genitourinary lesion at the onset of his illness; and although the cause of his death is not clear, it may well have been an overwhelming infection with a mycotic organism or a severe hemorrhage, or perhaps even a combination of the two.

Clinical Diagnosis: Aplastic anemia, presumably due to chloramphenicol; overwhelming infection, ? fungal in origin and/or hemorrhage.

PATHOLOGIC DISCUSSION

DR. RICHARD L. SWARM: There were striking numbers of petechiae and ecchymoses in the skin, and similar foci were present on all the serosal surfaces and in all the viscera. The femoral and vertebral bone marrows were light yellow and similar in appearance in both sites. The lungs were heavy, weighing 1,900 gm. There were nodular, dark red, firm areas in the lower lobes. The heart showed grey flecks scattered through the myocardium, and on the endocardium beneath the posterior leaflet of the mitral valve there was a soft, friable vegetation. The stomach and bowel contained dark material stained by partially digested blood. In the mucosa of the small intestine, as shown in Figure 1, there were small grey, ulcerated nodules covered by a thin fibrinous membrane. The liver, kidneys, mesenteric nodes and most other viscera also contained nodules of firm, homogeneous, yellow material as is shown in Figure 2. These nodules were of the consistency

[10] CLAUDON, D. B. and HOLBROOK, A. A. Fatal aplastic anemia associated with chloramphenicol therapy. *J. A. M. A.*, 149: 912, 1952.



1 2

FIG. 1. Grey nodules of monilial granulomas with overlying ulceration and hemorrhage in the ileum.

FIG. 2. Sharply outlined, firm granulomas in the liver and kidneys; these lesions were quite suggestive in their gross appearance of a metastatic tumor.

of tissue, and their sharp outlines gave them an appearance suggestive of metastatic tumor. The genitourinary tract was not remarkable grossly except that the urinary bladder had small ulcers and ecchymoses in its mucosa. The prostate was normal.

DR. ROBERT A. MOORE: There are three principal problems with which we should be concerned. First, the matter of the urinary tract infection or the prostatitis; second, the pancytopenia; and third, the nature of the nodules which were present in many of the solid viscera and the mucosa of the intestine.

Regarding the first problem Figure 3 illustrates a section of the urethra of this patient. The loose connective tissue beneath the transitional epithelium is infiltrated with a few small cells, and the blood vessels are prominent. This section, strictly speaking, represents a mild inflammatory reaction in the urethra; if one interprets this type of change as that of prostatitis, everyone over the age of forty or forty-five years has the disease. From a histologic viewpoint it lacks certain features which characterize true bacterial inflammation or infection. Particularly, cells are not seen migrating through the epithelium, such as is common in bacterial inflammatory conditions of other mucosal surfaces and in true acute prostatitis. I believe that the changes seen here might be called "physiologic inflammation," and that they are felated to the hormonal conditions and to the changes that the prostate undergoes with advancing age. Elsewhere in the prostate of this patient there was the typical tall, columnar epithelium of a young adult. The stroma was free of signs of inflammation; and if this man did have acute bacterial prostatitis when he was first treated, there was no evidence of it at the time of his death. In the remainder of the urinary tract we found no evidence of disease.

In respect to the pancytopenia we have studied particularly the sternal, vertebral and femoral bone marrow. The femoral bone marrow consisted of little but fat. Marrow typical of the sternum and vertebrae is shown in Figure 4. It is remarkably fatty and there is an edematous precipitate between the cells such as is characteristic of an acutely hypoplastic marrow. We were unable to find a megakaryocyte in any of the marrow sections. Among the cellular elements that were present (Fig. 5), 15 to 25 per cent were plasma cells. There was enough proliferative activity that a mitotic figure was found in almost every high power field. There were some hematopoietic elements, probably of both the erythroid and myeloid series, although they were difficult to identify with certainty; mitotic division was occurring in some of them. The majority of the cells were primitive, admixed with large numbers of plasma cells and lymphocytes. The lymph nodes showed the picture of exhaustion but no other changes.

At the time of autopsy we were a little puzzled by the nodules we found; the third problem in this case was whether the nodules represented tumor or some granulomatous infection. The question was rapidly resolved by smears, frozen sections and cultures, in all of which fungi were seen and specifically identified as Candida albicans. This patient, therefore, was suffering from disseminated moniliasis. The nodules in the intestine were necrotic foci of colonization of the organisms. The myocardium in Figure 6 shows a lesion in which the fungi

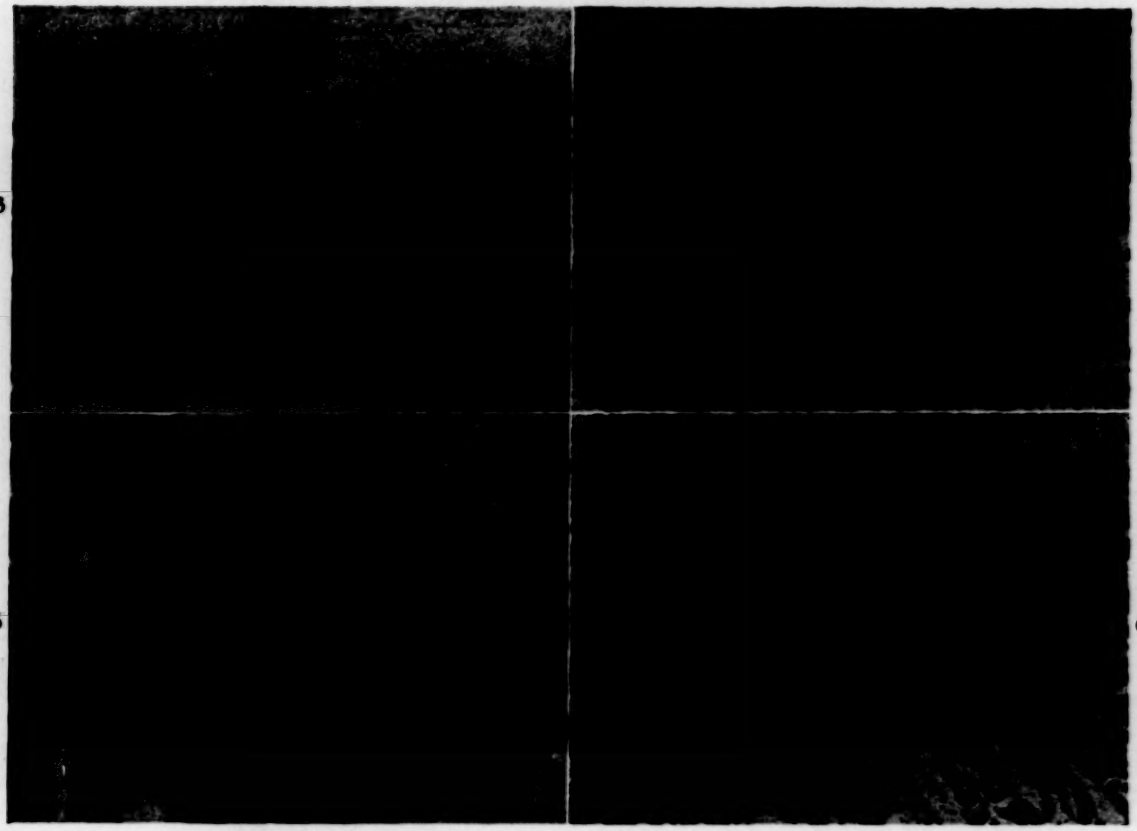


FIG. 3. "Chronic urethritis"; a common incidental finding that is a physiologic response to the hormonal and age changes of the urogenital epithelium and its stroma.

FIG. 4. Hypoplastic vertebral bone marrow typical of the most densely cellular regions of that organ; the persisting cells are mostly plasma cells and primitive cells.

FIG. 5. A high magnification of a clump of cells in the bone marrow showing the plasma cells and the mitotic figures that were commonly present.

FIG. 6. A focus of acute necrosis and growth of fungi in the myocardium.

were growing into the surrounding tissue without invoking any cellular reaction whatsoever. A higher magnification of this almost pure culture is shown in Figure 7. The mural vegetative endocarditis is shown in Figure 8 and probably resulted from the extension of a lesion within the myocardium. It undoubtedly contributed to the widespread dissemination of the fungi, although this man must have had a previous dissemination that established the lesion within the myocardium. The vegetation itself consisted only of organisms and fibrin.

In Figure 9 colonies of candida can be seen within an artery in the kidney. The colony in the upper left corner has the structure typical of fungi when they grow in necrotic tissue, while those which form the other mass in the center are identical in histologic structure to the mycotic vegetation in the heart. Outside the vessel is a cellular response of lymphocytes and plasma cells. Figure 10, also from the kidney, shows a lesion starting in a glomerulus; outward growth of fungi has produced acute necrosis without any cellular reaction.

Finally in other organs a hemorrhagic necrotizing pneumonia with many fungi but no cellular reaction was noted, and there was incidental and unexplained obstructive biliary cirrhosis of slight degree. The liver, spleen and kidneys showed no significant abnormalities, and certainly no damage from the blood transfusions.

In summary, from our observations, this man had pancytopenia as reflected by profound atrophy of the bone marrow. The presence of some mitoses indicated that the marrow was beginning to regenerate. The patient had received a variety of antibiotic drugs, at least two of which are known to be associated with this dyscrasia, but with our present state of knowl-

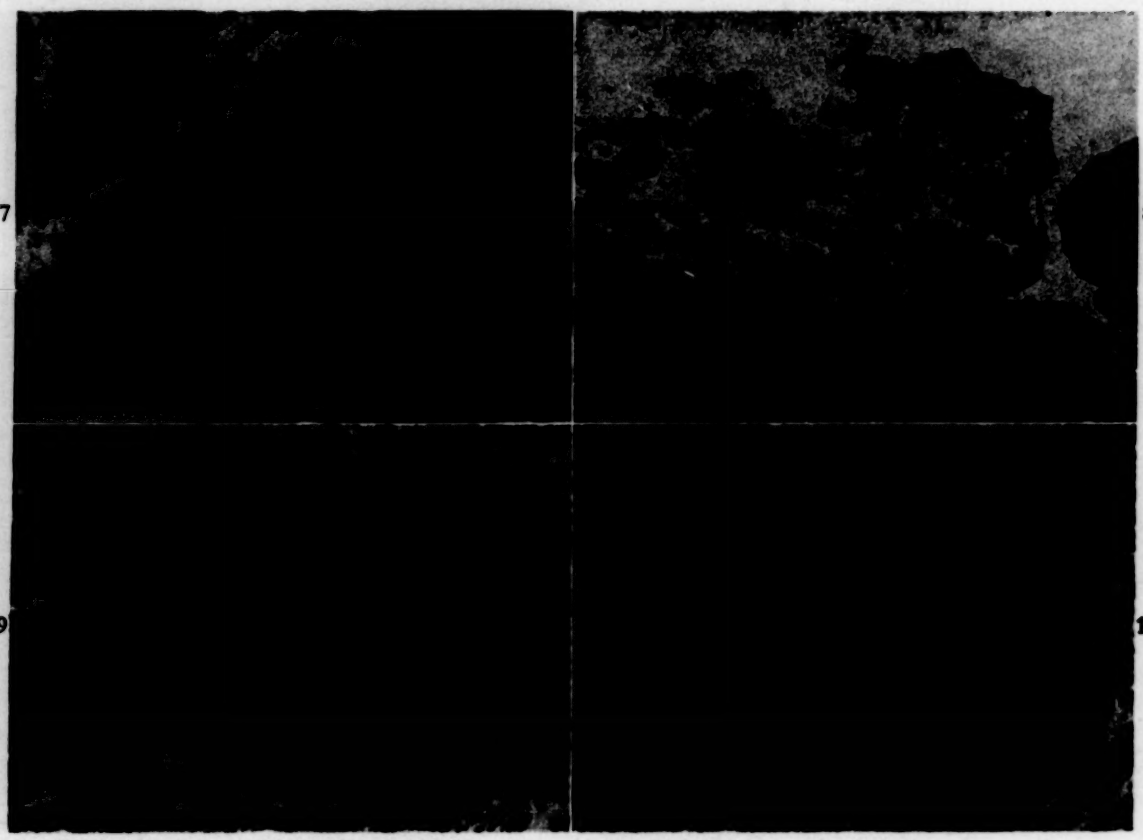


Fig. 7. An almost pure colony of Candida albicans in the myocardium.

Fig. 8. The endocardial vegetation of the posterior wall of the left ventricle; it is composed entirely of fibrin and fungi.

Fig. 9. Colonies of fungi within an artery in the kidney; the one near the center of the figure is identical in its histologic structure to the vegetation in the heart.

Fig. 10. A lesion arising and extending from a glomerulus; the granular material consists of blood and fungi.

edge we can do no more than note the coincidence of those facts. During the terminal period of his illness disseminated moniliasis developed. This complication has been observed to occur in other patients who have received long-continued courses of broad spectrum antibiotics. It is not certain that the pancytopenia contributed much to this last manifestation, for it occurs in patients who do not have leukopenia. The lack of cellular inflammatory response makes it difficult to estimate with accuracy the duration of this terminal phase, but it was undoubtedly short. At the time of death there remained no discernible evidence of the disease for which the patient originally was given antibiotics.

Final Anatomic Diagnoses: hypoplasia of the bone marrow, advanced; acute disseminated moniliasis; hemorrhage into the lumen of the stomach and intestine.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Autoimmune Hemolytic Disease and Cryoglobulinemia Associated with Chronic Lymphocytic Leukemia*

Hematologic and Metabolic Studies

ALBERT B. CRAIG, M.D., CHRISTINE WATERHOUSE, M.D. *and* LAWRENCE E. YOUNG, M.D.
Rochester, New York

THE object of this article is to report hematologic and metabolic studies in a case of chronic lymphocytic leukemia complicated by autoimmune hemolytic disease (symptomatic, acquired hemolytic anemia). Observations have been made over a period of seven years, with intensive study during a period of hemolytic crisis and during a period of partial remission from both the hemolytic and leukemic processes following administration of adrenocorticotrophic hormone (ACTH). Remission occurred on two separate occasions after use of the hormone and was sustained without maintenance therapy for about nine months after the first course and is currently (August, 1951) sustained six months after the second course.

Much less favorable results have been observed in this clinic in other cases of acquired hemolytic anemia after administration of ACTH. We have been impressed, moreover, with the frequency of spontaneous remissions of the hemolytic process in some cases studied over long periods of time. Evaluation of the therapeutic efficacy of ACTH (and cortisone) in the treatment of hemolytic and leukemic states is difficult and will not be attempted in this article. The chief purpose of this report is to describe the qualitative and quantitative changes observed in a single unusual case subjected to intensive study. Observations on other patients with autoimmune hemolytic disease in this clinic will be reported separately, especially with regard to serologic and therapeutic aspects.

Hematologic alterations produced by administration of ACTH and cortisone (compound E) in normal animals and men and in certain disease states have been described by other authors,[1–3] and the rationale for the use of these hormones in lymphocytic leukemia has been discussed.[4,5] Dameshek, Rosenthal and Schwartz[6] have reported eight cases of acquired hemolytic anemia (five idiopathic and three symptomatic) treated with ACTH. Amelioration of the hemolytic process occurred in each instance together with a fall in the titer of hemagglutinins in the serum and with reversal of the antiglobulin reaction in three cases. The rise in red blood cell count was attributed chiefly to a decrease in the rate of hemolysis as a result of diminution of antibody production or reactivity. Accelerated erythropoiesis was considered by these authors to be a possible additional factor in the response to ACTH. Gardner, McElfresh, Harris and Diamond[7] have also observed favorable response to administration of ACTH in eight cases of idiopathic acquired hemolytic anemia.

In the case to be reported herein red cell destruction was promptly decelerated following ACTH therapy; the rate of *in vivo* hemolysis was not well correlated, however, with the amounts of autoantibody demonstrable on the patient's red cells and in the patient's blood serum.

* From the Division of Cancer Research and the Department of Medicine of the University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial Hospital, Rochester, N. Y. This study was aided by grants from the Damon Runyon Memorial Fund for Cancer Research, the United States Public Health Service and by a contract between the Office of Naval Research, Department of the Navy and the University of Rochester (NR 131–174).

CASE REPORT

D. M., (also referred to in another report[8]) a fifty-four year old white female, was found to have chronic lymphocytic leukemia in June, 1944. During the next five years she tired easily but continued to do most of her housework. The only complication during this period was the development of chronic bronchitis which began in May, 1948. Enlarged cervical and axillary nodes were subjected to external radiation on five occasions with satisfactory response. Other nodes, the liver and the spleen were not palpable at any time.

The principal hematologic findings in this case are summarized in Figure 1. Between June, 1944, and June, 1949, the total white blood cell count varied from 50,000 to 70,000 except after radiation when it dropped to the range of 14,000 to 20,000. During the latter part of 1949 the white blood cell count rose progressively while the erythrocyte count declined; thirteen transfusions of 500 ml. each of whole blood were given during the period. In view of persistent reticulocytosis and the development of slight spherocytosis during January, 1950, a hemolytic process was suspected. The red cells were first tested with antiglobulin serum on January 5, 1950, and were found to give positive reactions. Osmotic and mechanical fragilities of the erythrocytes were first found to be significantly increased on February 5, 1950.

In the latter part of January, 1950, the patient became very weak; the cervical nodes became enlarged and painful and the rate of red cell destruction increased rapidly. On admission to the metabolic division on February 4, 1950, she was severely ill. There was enlargement of cervical and axillary nodes but the liver and spleen could not be felt. The temperature was 38.7°C. Bronchopneumonia had developed in the right lower lobe. The white blood cell count was 112,000, erythrocyte count 2.12 million, hematocrit 16.8 per cent and reticulocytes 2.9 per cent. The differential count of the white cells was as follows: segmented neutrophils 8; small, mature lymphocytes 87 and lymphocytes of intermediate size 5 per cent. Platelets were present in normal numbers. Approximately 5 per cent of the red cells appeared spheroidal and 2 to 3 per cent showed diffuse basophilia.

Methods and Plan of Metabolic Study

The methods and plan of metabolic study were as follows: Metabolic studies were carried out during thirteen periods of five days each in February, March and April, 1950. The diet, twenty-four-hour urine specimens and pooled five-day stool specimens were analyzed for content of nitrogen, chloride, phosphorus, calcium, sodium and potassium, according to the technics outlined previously.[9] Fecal urobilinogen determinations[10] were carried out on the stool samples from each period and are recorded in milligrams of urobilinogen per day. The hemolytic index, $\frac{\text{mg. fecal urobilinogen per day}}{\text{total circulating hemoglobin in gm.}} \times 100$, was computed by the formula of Miller, Singer and Dameshek[11] (normal range = 11 to 21 mg. per 100 gm. hemoglobin per day). All blood transfused was collected in acid-citrate-dextrose medium and stored at 4°C. for one to three days before use. Serum from each donor was tested in order to eliminate those with anti-A antibodies having high titer and immune characteristics.[13]

Blood from the patient was drawn daily between 8:00 and 9:00 A.M. for hematologic and chemical determinations. Methods for differential agglutination of red cells[12] and for measurement of antiglobulin titer[8,14] and osmotic[15] and mechanical fragility[16] of erythrocytes are described elsewhere. Determinations of hematocrit were made by the Wintrobe method. Reticulocytes were stained with brilliant cresyl blue and the per cent of the patient's own red cells that were reticulocytes at any given time was computed by assuming that all of the donated red corpuscles in the patient's circulation were mature.

The plan of study was dictated by the course of the patient's illness. During period I the patient was suffering from bronchopneumonia. Her intake during these five days consisted only of ginger ale. From the beginning of period II until the end of period XIII, however, the dietary intake was constant, the same food being consumed each day. Repeated analyses showed that the day's ration of 2,254 calories contained 15.71 gm. nitrogen, 1.52 gm. phosphorus, 83 mEq. potassium, 174 mEq. sodium and 168 mEq. chloride.

It was originally planned to give blood transfusions only at the start of the experiment. After ten days it became obvious, however, that the patient would require more blood. An attempt was therefore made to transfuse sufficiently often and in large enough quantities to maintain the hematocrit at a nearly constant figure starting with period III.

The hematocrit and total red blood cell count were fairly well stabilized after twenty more days of this program, that is, at the end of period VI when ACTH therapy was instituted. The patient received 100 mg. of ACTH each day (Armour Standard LA-1-A control No. H7511 List 3185) in four divided doses during periods VII and VIII, and during period IX the dose was reduced to 50 mg. per day. The same lot of ACTH was used throughout. No ACTH was given during the last four periods of metabolic study. Bronchopneumonia recurred during period XII, necessitating the use of aureomycin for five days. A total of sixty-five days, or thirteen five-day periods, were spent on the metabolism division.

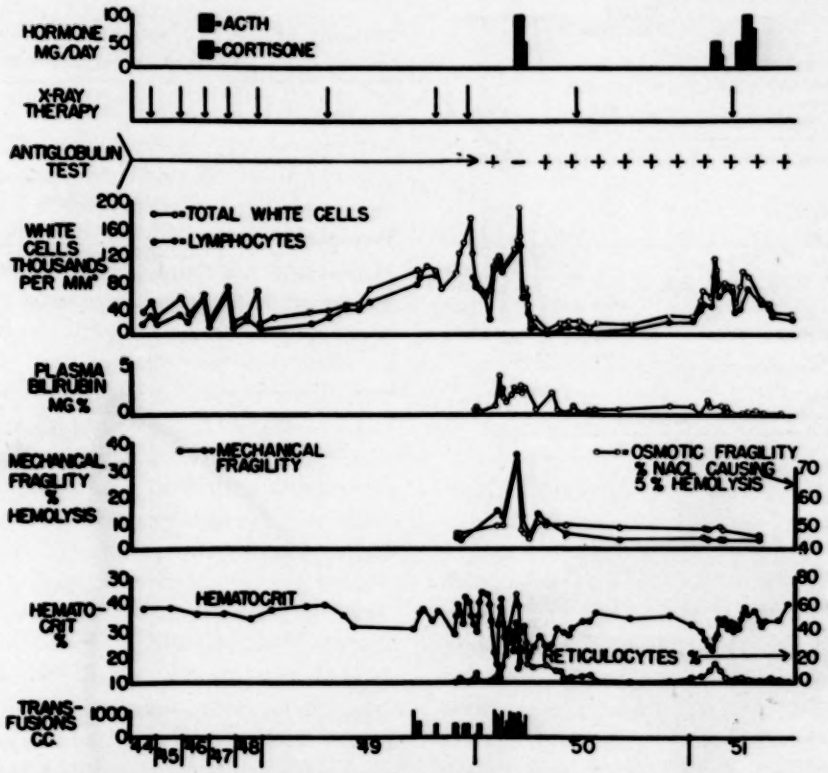


FIG. 1. Summary of principal laboratory findings in relation to therapy over period of seven years in case of D. M. Transfusions given in 1949 are recorded as cc. of whole blood; transfusions in 1950 are recorded as cc. of red blood cells.

Clinical Course

The clinical course was as follows: During the thirty days required for control study on the metabolism division the patient was ambulatory but she experienced some lassitude, headache and anorexia when the hematocrit fell below 24 per cent. Administration of ACTH was complicated by the retention of extracellular fluid, the dose of the hormone being reduced by one-half on the tenth day because of the development of marked edema. The lymph nodes began to regress after four days of ACTH therapy and became barely palpable by the fifteenth day.

When ACTH was discontinued, there was an immediate diuresis and a weight loss of 5.8 kg. associated with loss of all edema. Although the concentration of potassium in the serum promptly rose to normal levels, weakness disappeared slowly. Clinical improvement was progressive, however, (except for an intercurrent infection in period XIII) and by the end of twenty days after ACTH was discontinued her appetite was good and she was able to carry on moderate activity.

Since conclusion of the metabolic study the patient has had several episodes of bronchopneumonia and roentgenograms of the chest after instillation of lipiodol have revealed evidence of bronchiectasis in both lower lobes. Until January, 1951, the cervical and axillary lymph nodes enlarged but little, the total white cell count remained below 20,000 and the hematocrit was maintained at 35 to 38 per cent

without transfusion. She tired easily but was ambulatory and did light housework during this period.

In January, 1951, the cervical and axillary lymph nodes enlarged considerably and the total white cell count rose to 66,000 while the

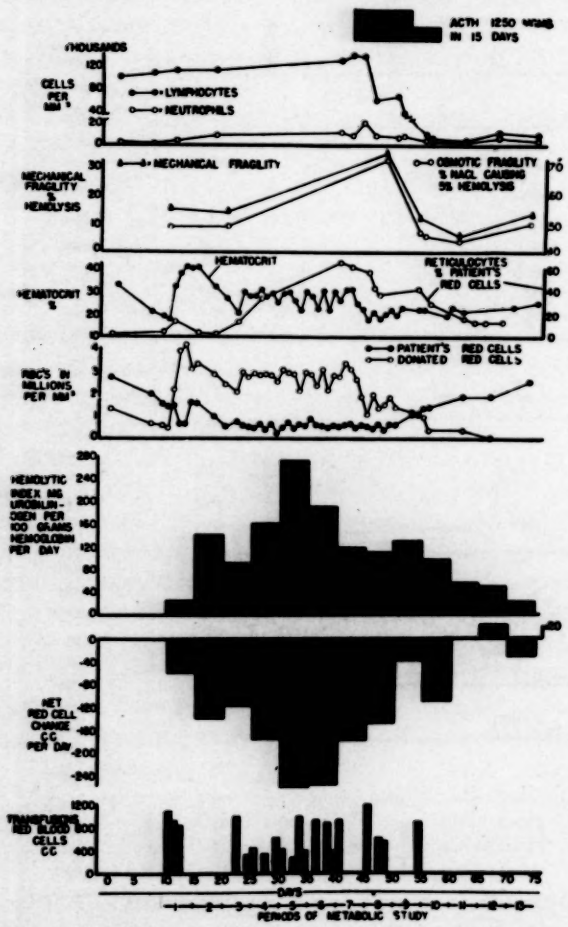


FIG. 2. Hematologic alterations in case of D. M. immediately before and during metabolic study.

hematocrit fell to 23 per cent and the reticulocytes increased to 9 per cent. She was admitted to the hospital on January 31st and remained until March 30th. During this admission she received a total of 1,150 mg. of ACTH over periods totaling twenty-five days. (Fig. 1.) The hematologic response was less dramatic than in March, 1950, due perhaps in part to the fact that she was less acutely ill than at the start of the metabolic study. The slower response in 1951 might also be attributed to the smaller dose used, namely, 50 mg. per day for twenty-one days and 25 mg. per day for four days. No edema developed during this period.

Since the cervical and axillary lymph nodes did not regress promptly after use of ACTH, x-ray therapy was again applied daily to these areas from March 7th to March 17, 1951. The nodes then became barely palpable and have not since enlarged. Cortisone was given orally in doses of 100 mg. per day from March 30th to April 14th and in doses of 75 mg. per day from April 15th to April 20, 1951. Cortisone was given with the hope of maintaining hematologic improvement, but the patient's cough became worse as had previously been noted during ACTH therapy. She was readmitted to the hospital from April 28th to June 6, 1951, because of a severe bout of bronchopneumonia which responded slowly to administration of antibiotics and sulfonamides. The partial hematologic remission has been well sustained (Fig. 1) but chronic cough and intermittent fever persist as of August, 1951.

TABLE I
SUMMARY OF DATA ON NET RED CELL CHANGE AND FECAL UROBILINOGEN EXCRETION

Period	Red Cells Transfused (cc./period)	Net Red Blood Cell Change (cc./period)	Change in Red Cell Mass (cc./period)	Fecal Urobilinogen (mg./day)	Hemolytic Index (mg. urobilinogen per 100 gm. hg./day)
I	1566	−296	+1270	122	24.5
II	0	−770	−700	333	142.0
III	811	−591	+220	536	92.8
IV	803	−883	−80	720	173.0
V	1182	−1317	−135	918	272.0
VI	1315	−1285	+30	772	191.5
VII	531	−991	−470	464	118.5
VIII	1276	−746	+530	575	110.0
IX	512	−192	+320	715	132.5
X	0	−550	−550	292	98.2
XI	0	0	0	181	55.0
XII	0	+120	+120	148*	49.8
XIII	0	−140	−140	70*	22.5

* The amount of urobilinogen excreted in the stool during Periods XII and XIII was quite likely reduced by oral administration of aureomycin.

Hematologic Results

The principal hematologic findings during the period of metabolic study are shown in Figure 2 and Table I.

Estimates of the net red blood cell change

(i.e., the difference between the volume of red blood corpuscles produced per unit time and the volume destroyed in the same unit of time) were made on the basis of the volumes of transfused red blood cells required to keep the red blood cell mass constant. Red blood cell mass was calculated from determinations of the hematocrit and plasma volume.

$$\frac{\text{Plasma volume} \times \text{hematocrit}}{100 - \text{hematocrit}} = \text{red cell mass.}$$

The net body red cell change was then calculated as red blood cell mass (end of period) − red blood cell mass (start of period) − volume of red blood cells infused. The roughness of these calculations is fully realized, particularly with respect to plasma volume, which was assumed to be a constant part of the extracellular fluid. However, the changes in extracellular fluid were negligible at all times except during the period of administration and withdrawal of ACTH when gain balanced eventual loss.

During periods II, III and IV there was a deficit of between 140 and 160 cc. of cells per day. (Table I, column 2.) The negative balance became more marked in periods V and VI at which time the rate was about 260 cc. of cells per day. While receiving ACTH the loss became progressively less and in the control periods after ACTH therapy the rates of red cell production and destruction became nearly equal. No transfusions have subsequently been required.

The plot of net red blood cell change in Figure 2 is nearly a mirror image of the plot of the hemolytic indices; both plots reflect changes in the rate of red cell destruction. Hemolytic indices could not be determined accurately during the subsequent periods of observation in 1950 and 1951 because the bacteria responsible for conversion of bilirubin to urobilinogen in the intestine were greatly reduced in numbers by oral administration of antibiotics (aureomycin and terramycin).

During the period of metabolic study the patient's washed erythrocytes were tested every two or three days with serial dilutions of antiglobulin rabbit serum; tests have subsequently been made at intervals of two days to two weeks. Because of difficulties inherent in quantitation of the antiglobulin reaction, the results of these titrations are not included in Figure 2. It is noteworthy, however, that the reactions became negative for a period of nine days, starting with the tenth day of the first course of ACTH therapy in March, 1950. The reactions have since been of moderate strength as they were constantly before therapy and they were not appreciably modified by administration of ACTH and cortisone during February, March and April, 1951. Antibody eluted from the patient's red cell stroma sensitized normal red cells for the antiglobulin reaction and directly agglutinated trypsinized normal red cells of all types tested.[8,17]

There was a sharp rise in both osmotic and mechanical fragility of the red cells between the twentieth and forty-fifth days of the period covered by the graph of Figure 2. During this period the rate of red cell destruction increased substantially, as indicated by the brisk reticulocytosis, low count of the patient's red cells, heavy requirement for transfused red cells and the increased excretion of urobilinogen in the feces. The serum bilirubin concentration varied from 2.0 to 3.0 mg. per cent at this time but there was no hemoglobinemia and no absorption band in the red portion of the spectrum (indicative of methemalbuminemia) could be seen on repeated examinations of the serum.

From the first to the tenth and from the thirteenth to the twenty-second days of the period covered by Figure 2 no transfusions were given. The slopes of the decay curves for donated cells and the patient's cells during these periods indicate that the donated cells and the patient's own cells were being destroyed rapidly and indiscriminately. Smears of capillary blood drawn during the periods of most active red cell destruction revealed that nearly all of the red cells (including the donated corpuscles) that were not reticulocytes had become spheroidal. Spherocytes became much less numerous after ACTH therapy but approximately 3 to 5 per cent of the red cells appeared spheroidal until May 18, 1950. Subsequent smears and wet preparations have revealed little or no spherocytosis. Figures for osmotic and mechanical fragility of the red cells have since remained in or near the normal range even during the period of increased hemolytic activity in January and February, 1951. (Fig. 1.)

There was substantial reticulocytosis prior to ACTH therapy both in March, 1950, and in February, 1951. It is, therefore, likely that amelioration of the anemia following therapy was due largely to deceleration of red cell destruction rather than to acceleration of erythropoiesis. During the first ten days of ACTH therapy in February, 1951, however, reticulo-

cytes gradually increased from 9 to 16 per cent, suggesting some enhancement of red cell formation.

Fluctuations in the leukocyte counts in relation to ACTH and other therapy are shown in Figures 1 and 2. The decline in lymphocytes was less striking during and after the second course of ACTH than after the first. The total white cell count actually increased from 66,000 to 103,000 during the first eight days of the second course in February, 1951, and thereafter the decline in count was relatively slow. The proportion of lymphocytes in the smear was not significantly altered during administration of ACTH and cortisone in 1951.

Eosinophils ranged from 0 to 3 per cent before and during the first course of ACTH and have subsequently varied from 0 to 10 per cent. Counts of 0 to 0.5 per cent were obtained before and during the second period of ACTH (and cortisone) administration in 1951. There has recently been some correlation between the degree of eosinophilia and the severity of bronchitis and bronchopneumonia. Enumeration of eosinophils in the counting chamber has been difficult because of aggregation of white cells in small lumps of cryoglobulin.

Serum and Plasma

The titer of hemolytic complement in the serum has remained within the normal range. Cold hemagglutinins and incomplete warm antibodies (capable of agglutinating trypsinized normal red cells or of sensitizing normal red cells for the antiglobulin reaction) have been detected at times in very low titer but hemolysins have never been demonstrable, even in tests with trypsinized cells.[8,18] The various reactions of the serum with normal red cells have in general been too weak for measurement in relation to therapy. The possibility that the large amount of cold precipitable globulin present in the serum might interfere with the serologic reactions has not yet been entirely excluded. Cryoglobulin[19] was first demonstrated in the patient's blood on November 26, 1949, and has since been constantly present. The total protein concentration in the serum has been approximately 0.7 gm. per 100 cc. lower in clotted blood maintained at 4°c. than in that kept at 40°c. prior to determinations by the Kjeldahl method. Blood drawn into oxalate has invariably shown gel formation within five to ten minutes at room temperatures of 22° to 28°c. Storage of plasma or serum at 4°c. has regularly produced large gelatinous masses within ten to thirty minutes. The gels have been readily liquefied by warming to 37 to 40°c.

Dr. Eric Alling studied the electrophoretic patterns of the plasma on ten occasions between November 26, 1949, and April 11, 1950. His observations were as follows (personal communication): "The concentration of gamma globulin was always low (0.4 ± 0.1 gm. per 100 cc.). In four of the ten patterns there was a small abnormal peak migrating more slowly than gamma globulin. This probably represented a complex between a cryoglobulin and gamma globulin. The possibility of such complex formation is rendered more likely by the fact that the isoelectric point of the cryoglobulin was 8.6 as determined by the pH of minimum solubility and by precipitation by an anionic detergent. It is probable that the variations in the gamma globulin concentrations were due to occasional incomplete precipitation of the cryoglobulin during the period in which the plasma stood at 4°c. prior to dialysis. The fibrinogen concentration was 25 per cent above normal before the first course of ACTH and during therapy decreased to 50 per cent of the original figure."

Results of Metabolic Studies

The nitrogen, phosphorus, calcium, sodium, chloride and potassium balance data are given in Table II and Figure 3. The gross balances were calculated in the usual way, i.e., intake was considered to consist of food, transfused cells and plasma. Output was measured in the urine, stool and blood withdrawn for study. Since considerable and variable percentage of the intake was contained in the blood given, analysis of the transfused red cells was of importance.

Thirteen different lots of pooled blood amounting to a total of 8 L. of red cells were used in transfusing this patient during the period of metabolic study. Each pool was analyzed for content of nitrogen, sodium, potassium, chloride, phosphorus and calcium; plasma and whole blood were analyzed separately. The hematocrit of each pool was also determined. The average values for the aforementioned elements found in the red cells are listed in Table III. The specific values for each pool were used in computing the gross balance at the time the blood was given.

Calculations of gross balances did not take into account the changes of red cell mass which were known to have occurred. Although these changes were not great except during periods I and II, the nitrogen content of the red blood cells was high enough to cause significant changes in the gross balance even when rather small volume changes occurred. The calculations of changes in red cell mass have already been described and the figures obtained are given in Table I, column 3. The amounts of the elements with which we were concerned in the transfused red blood cells were determined from the average analytical values and subtracted from the gross balance figures. The net balance thus computed provided a correction of the gross balance for failure to maintain a constant red cell mass. Since the net balance figures were considered the best possible indices of general metabolic changes in this case, only these figures will be considered in the remainder of the discussion. (Table II, Fig. 3.)

During the control study the patient was in

TABLE II

SUMMARY OF DATA ON BALANCE STUDIES

Period	Blood Transfused	Gross Balance	Net Cell Balance	Net Balance	Blood Transfused	Gross Balance	Net Cell Balance	Net Balance	Blood Transfused	Gross Balance	Net Cell Balance	Net Balance
	Nitrogen (gm.)				Phosphorus (gm.)				Calcium (gm.)			
I	82.0	+24.7	+58.6	−33.9	1.20	−0.58	+0.84	−1.42	0.11	−0.71	0	−0.71
II	0	−3.1	−35.5	+32.4	0	+1.97	−0.51	−2.48	0	+0.48	0	+0.48
III	43.3	+26.2	+10.2	+16.0	0.66	+1.68	+0.15	+1.53	0.03	+0.14	0	+1.41
IV	41.9	+18.4	−3.7	+22.1	0.55	+1.10	−0.05	+1.15	0.04	+0.62	0	−0.62
V	52.0	+5.3	−6.2	+11.5	0.81	+0.96	−0.09	+1.05	0.06	+0.03	0	+0.03
VI	68.7	+14.7	+1.4	+13.3	0.88	+0.64	+0.02	+0.62	0.09	−0.24	0	−0.24
VII*	31.2	−43.6	−21.7	−21.9	0.46	−2.49	−0.31	−2.18	0.03	+0.89	0	+0.89
VIII*	66.9	−26.0	+24.5	−50.5	0.83	−4.08	+0.35	−4.43	0.05	−1.21	0	−1.21
IX†	26.9	−33.3	+14.8	−48.1	0.35	−1.16	+0.21	−1.37	0.02	+0.18	0	+0.18
X	0	−21.0	−25.4	+4.4	0	−0.61	−0.36	−0.24	0	−1.02	0	−1.02
XI	0	−5.7	0	−5.7	0	+0.42	0	+0.42	0	+1.17	0	+1.17
XII	0	−18.2	+5.5	−23.7	0	−3.88	+0.08	−3.96	0	−6.29	0	−6.29
XIII	0	+5.2	−6.5	+11.7	0	−0.29	−0.09	−0.29	0	−2.41	0	−2.41

Period	Chloride (mEq.)				Sodium (mEq.)				Potassium (mEq.)			
I	143	−10	+66	−76	204	−31	+16	−47	125	+19	+96	−75
II	0	+201	−49	+250	0	+184	−10	+194	0	+172	−58	+230
III	74	+148	+11	+137	86	+160	+2	+158	68	+118	+17	+101
IV	74	−72	−4	−68	87	−66	−1	−65	69	+135	−6	+141
V	106	−27	−7	−20	144	+3	−2	+5	98	+138	−10	+148
VI	122	+72	+2	+70	144	+109	0	+109	109	+137	+2	+135
VII*	53	+373	−25	+398	62	+610	−6	+616	45	−123	−35	−88
VIII*	123	+550	+28	+522	122	+699	+7	+692	107	−141	+40	−181
IX†	46	+6	+17	−13	54	+147	+4	+143	42	−37	+24	−61
X	0	−576	−19	−557	0	−1094	+7	+1087	0	+151	−41	+191
XI	0	−15	0	−15	0	−111	0	−111	0	+65	0	+65
XII	0	−138	+6	+144	0	−124	+2	−126	0	+22	+9	+13
XIII	0	+106	−7	+113	0	+133	−2	+135	0	+16	−11	+27

* ACTH was administered in dose of 100 mg. daily during this period.
† ACTH was administered in dose of 50 mg. daily during this period.

positive *nitrogen balance* (10 to 20 gm. per period) with the exception of period I. At that time (period I) the patient was receiving no nitrogen in her diet and the negative figure was to be expected. While receiving ACTH the patient exhibited a negative nitrogen balance to a

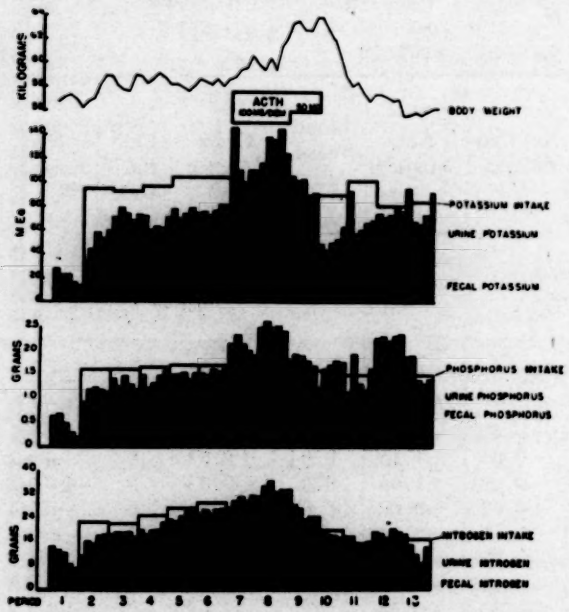


FIG. 3. D. M., age fifty-two, female, unit No. 127082. Body weight; potassium, phosphorus and nitrogen balances. Intake indicated by solid line. Output extending above the intake indicates negative balance; below, positive balance. ACTH 100 mg. per day given in period VII and VIII, 50 mg. per day in period IX.

marked degree. The total nitrogen lost during the three periods was 120 gm. It is evident that the patient was returning to positive balance in period X. The temporarily negative balance seen in period XII was undoubtedly caused by a pneumonic process which she developed.

The *phosphorus balances* followed closely the pattern of nitrogen throughout; in fact, the calculations of the theoretic nitrogen balances from calcium and phosphorus (with the exception of periods VII and IX) agreed remarkably well with the actual nitrogen balance when the net figures for both were considered. (Table IV, column 4.)

There was no consistent trend or change noted in the calcium balance. Beginning in period IX urinary excretion of calcium increased from an average control figure of 0.210 gm. per period (periods I to VI) to an average of 0.380 gm. of calcium per period for the last five periods (periods IX to XIII).

Chloride balances are recorded in Table II. The fluctuations seen during the control periods were not great. The patient retained 398 mEq. of chloride during the first five days of ACTH and even a greater amount, 522 mEq., was retained in the following period. After reduction

TABLE III
SUMMARY OF DATA ON ANALYSES OF THIRTEEN LOTS OF POOLED RED BLOOD CELLS TRANSFUSED TO PATIENT, D. M.

	Mean	Standard Deviation	Range
Nitrogen gm./L.	46.14	±1.47	43.08–48.55
Sodium mEq./L.	12.9	±3.1	6.2–16.6
Potassium mEq./L.	75.4	±3.2	69.5–80.7
Chloride mEq./L.	52.3	±4.5	43.7–58.9
Phosphorus gm./L.	0.66	±.10	0.55–0.89

of the dosage of ACTH a loss of 13 mEq. was seen. Withdrawal of the hormone produced a deficit of 557 mEq. in a five-day period.

The extracellular fluid volume (ECF) was calculated from the chloride balance and the change in concentration of chloride in the serum as described by Elkington et al.[20] and the results are seen in Table IV, column 1.

The fluctuations during the control periods were small, but during three periods of ACTH therapy there were gains of 2.0, 4.9 and 0.6 L., respectively, for periods VII, VIII and IX or a total gain of 7.5 L. During the first period after ACTH the patient lost 5.7 L.

The amount of sodium unaccounted for by changes in extracellular fluid is recorded in Table IV, column 2. During periods VII and IX much more sodium than chloride was retained and during periods X and XI more sodium than chloride was lost.

Potassium balances are shown in Table II. In periods II to VI there was a definite retention of potassium in amounts of 101 to 230 mEq. per period. While receiving ACTH the patient lost a total of 330 mEq. potassium, gaining 256 mEq. in the first two periods after the drug was stopped.

The theoretic nitrogen balances were calculated, using the net potassium balances corrected for changes in extracellular fluid and the generally accepted ratio, N:K = 1 gm.:2.7 mEq.

The results of these calculations are shown in Table IV, column 5. For the most part there was much greater retention of potassium than could be accounted for by nitrogen balances alone.

Electrolyte concentrations as determined in serum samples are graphed in Figure 4. The rise in serum sodium and chloride, as well as the simultaneous fall of serum potassium and phosphorus during ACTH therapy, should be noted.

TABLE IV

SUMMARY OF DATA PERTAINING TO SODIUM AND POTASSIUM EXCHANGE

Period	Extracellular Fluid		Sodium Unaccounted for by Change in Extracellular Fluid (mEq.)	Nitrogen Balance (gm.)	Theoretical Nitrogen Balance		Potassium Unaccounted for by Gain or Loss of Protein (mEq.)
	Total at End of Period (L.)	Gain or Loss During Period (L.)			From Phosphorus (Corrected for Calcium) (gm.)	From Potassium (gm.)	
I	10.4	−0.2	+100	−33.9	−15	−28	+17
II	11.6	+1.2	+16	+32.4	+30	+84	+141
III	12.7	+1.1	−52	+16.0	+21	+36	+58
IV	11.8	−0.9	+29	+22.1	+19	+53	+82
V	11.1	−0.7	+78	+11.5	+14	+54	+118
VI	12.3	+1.2	−72	+13.3	+10	+49	+99
VII*	14.3	+2.0	+158	−21.9	−35	−33	−29
VIII*	19.2	+4.9	−59	−50.5	−52	−67	−45
IX†	19.8	+0.6	+118	−48.1	−19	−20	+69
X	14.1	−5.7	−75	+4.4	+3	+70	+180
XI	14.2	+0.1	−173	−5.7	−1	+24	+80
XII	12.5	−1.7	+95	−23.7	−15	+5	+77
XIII	13.5	+1.0	−48	+11.7	+13	+11	−5

* ACTH was administered in dose of 100 mg. daily during this period.

† ACTH was administered in dose of 50 mg. daily during this period.

COMMENTS

The mechanisms responsible for the shortened life span of both donated red corpuscles and the patient's own red cells are not clearly understood. In twelve cases of autoimmune hemolytic disease (acquired hemolytic anemia) studied in our laboratory there has been relatively little correlation between the rate of *in vivo* hemolysis and the results of various quantitative tests for measuring autoantibody in the serum and attached to the patient's red cells.[8,17] Other observers have had variable experience in this respect.[6,7,18,21] It is unfortunate that in D. M.'s case autoantibody has been detectable in the serum in amounts too small to measure in relation to the rate of red cell destruction.

Hemolysins, which could reasonably be expected to produce hemolysis *in vivo*,[18] could not be detected in the serum of D. M. Since hemoglobinemia was not a feature of her illness, it is unlikely that intravascular hemolysis occurred to any great extent. A number of mechanisms might be suggested to explain the *in vivo* effect of non-lytic antibodies, such as those demonstrable on the red cells and at times in the serum of D. M. Such antibodies might damage the erythrocytes more slowly than lysins or cause increased susceptibility of the red cells to trapping and lysis within the spleen.[8,17,22] They might also render the red cells more liable to phagocytosis by cells of the reticuloendothelial system.[23] Another possibility suggested by the experiments of Castle, Ham and Shen[24] is that antibodies causing *in vitro* agglutination may produce the following sequence *in vivo:* intravascular agglutination of red cells, erythrostasis, tissue ischemia and release from autolyzing tissues of substances injurious to red cells.

The stimulus for production of autoantibodies in both idiopathic and symptomatic cases of acquired hemolytic anemia is unknown. Although such antibodies are often encountered in patients who have never been given a transfusion, the course of events in the case of D. M. suggests that the transfusions of whole blood in 1949 might have played a part in activating the

hemolytic process. Experience in this case and in others studied in this clinic[17] further suggests that once the hemolytic disorder has become active, withholding of transfusions may at times be desirable in an attempt to decelerate red cell destruction. This aspect of autoimmune hemolytic disease deserves much more investigation.

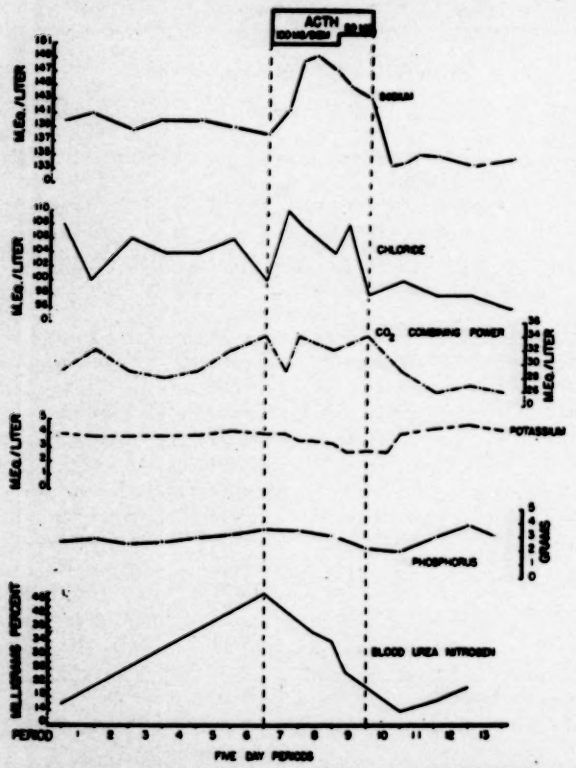


FIG. 4. D. M., age fifty-two, female, unit No. 127082. Serum electrolytes before, during and after ACTH.

In this clinic and elsewhere, patients with hemolytic anemia of the type described in this report have experienced remissions spontaneously (i.e., without therapy), after radiation of superficial lymph nodes, after splenectomy and after administration of ACTH. It is impossible at present to state precisely how remission is brought about in any of these instances. The effects of ACTH and coristone on lymphoid tissue,[3–5,22] on antibody production[6,26–28] and on the phagocytic action of the reticuloendothelial cells[29] are subjects of continuing debate. Further observations obviously will be necessary in order to achieve a more complete understanding of the action of these hormones in decelerating red cell destruction in the autoimmune hemolytic disorders.

Marked and sustained reduction in the number of circulating lymphocytes and in the size of lymph nodes in patients with chronic leukemia seldom occurs without treatment but is often seen after radiation therapy. Similar results have recently been observed in some cases after administration of ACTH or cortisone.[4,5] In the case of D. M. response of the lymphoid tissue to the first course of ACTH was prompt and prolonged after only fifteen days of therapy although response to the second course eleven months later was less dramatic. Although evaluation of hormonal therapy in chronic lymphocytic leukemia is difficult, it seems likely that in cases complicated by a hemolytic process the hormone has a double target, namely, lymphoid tissue and autoantibody formation (or reactivity). Relationship of the lymphoid structures to antibody production may in fact be elucidated by further studies on cases of this type.

The metabolic effects of ACTH observed in this patient were qualitatively in keeping with known results of adrenal cortical stimulation, namely, the production of negative nitrogen, phosphorus and potassium balances and retention of sodium and chloride.[30–32] The quantitative relationships in the movements of these substances, on the other hand, followed a somewhat unexpected pattern. ACTH has been shown experimentally to promote the catabolism of protein (which would cause excretion of all intracellular elements) and to stimulate gluconeogenesis (which would cause retention of potassium and probably phosphorus). In any balance study ACTH would therefore increase nitrogen excretion without proportionately increasing phosphorus and potassium excretion. This has been found to be true in two patients with hypopituitarism.[32] An exchange of potassium and sodium in the cells on both initiation and withdrawal of ACTH has also been demonstrated.

Changes in phosphorus and potassium balance that occurred in this patient were explainable by neither of the aforementioned mechanisms. This pattern of change has been seen in this clinic in one other patient suffering from reticulum cell sarcoma treated with ACTH in similar dosage. During the first five days of ACTH administrations in the case of D. M., 26 mm. of phosphorus and 29 mEq. of potassium were excreted in excess of the amounts that should have been excreted with nitrogen. With reduction of the dose of ACTH to 50 mg. daily, there was abrupt moderation of potassium and phosphorus losses although excretion of nitrogen continued un-

abated. It is interesting that the deposition of intracellular sodium continued during this time. On withdrawal of the drug a prompt excretion of intracellular sodium and retention of potassium occurred although the phosphorus balance re-established its normal relationship with nitrogen.

The loss of both intracellular cations and anions without equivalent loss of nitrogen, which was seen when 100 mg. of ACTH was given daily, may have been related to the destruction of leukemic cells. When the dose was reduced to 50 mg. daily, there was a conspicuous lack of excretion of potassium and phosphorus in amounts anticipated from the nitrogen balance. This discrepancy might be accounted for by assuming that these elements were stored with glycogen.

In stimulating the various functions of the adrenal gland, the effect of ACTH may vary widely, possibly depending upon dose and length of time administered and upon the clinical state of the patient.

SUMMARY

1. Hematologic and metabolic studies were made before, during and after administration of ACTH in a case of chronic lymphocytic leukemia complicated by autoimmune hemolytic disease and cryoglobulinemia.

2. Reduction in the number of circulating lymphocytes, in the size of the peripheral lymph nodes and in the rate of red cell destruction was sustained for nine months following administration of 1,250 mg. of ACTH over a period of fifteen days. Response following a second series of injections of ACTH was less dramatic but was again well sustained. The possible mode of action of ACTH in this case is briefly discussed, with particular reference to effects on lymphoid tissue and on production or reactivity of autoantibody.

3. During ACTH therapy the expected loss of nitrogen, phosphorus and potassium occurred. The quantitative exchange of these substances, however, was believed to have been influenced by the destruction of malignant tissue as well as by the other known metabolic effects of this hormone.

REFERENCES

1. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Staehelin, D. and Wilson, D. L. The clinical usefulness of ACTH and cortisone. *New England J. Med.*, 242: 783–793; 824–834; 865–872; 1950.
2. Hills, A. G., Forsham, P. H. and Finch, C. A. Changes in circulating leukocytes induced by the administration of pituitary adrenocorticotrophic hormone (ACTH) in man. *Blood*, 3: 755–768, 1948.
3. Dougherty, T. F. and White, A. Influence of hormones on lymphoid tissue structure and function. The role of the pituitary adrenocorticotrophic hormone in the regulation of the lymphocytes and other cellular elements of the blood. *Endocrinology*, 35: 1–34, 1944.
4. Pearson, O. H. and Eliel, L. P. Use of pituitary adrenocorticotrophic hormone (ACTH) and cortisone in lymphomas and leukemias. *J. A. M. A.*, 144: 1349–1353, 1950.
5. Saunders, R. H., Zannos, L. and Dameshek, W. The use of ACTH therapy in the treatment of leukemia. Proceedings of the Third International Hematology Congress, Cambridge. New York, 1950. Grune & Stratton.
6. Dameshek, W., Rosenthal, M. C. and Schwartz, L. I. The treatment of acquired hemolytic anemia with adrenocorticotrophic hormone (ACTH). *New England J. Med.*, 244: 117–127, 1951.
7. Gardner, F. H., McElfresh, A. E., Harris, J. W. and Diamond, L. K. The effect of adrenocorticotrophic hormone (ACTH) in idiopathic acquired hemolytic anemia as related to the hemolytic mechanisms. *J. Lab. & Clin. Med.*, 37: 444–457, 1951.
8. Young, L. E., Miller, G. and Christian, R. M. Clinical and laboratory observations on autoimmune hemolytic disease. *Ann. Int. Med.*, in press.
9. Waterhouse, C., Bassett, S. H. and Holler, J. W. Metabolic studies on protein depleted patients receiving a large part of their nitrogen intake from human serum albumin administered intravenously. *J. Clin. Investigation*, 28: 245–264, 1949.
10. Schwartz, S., Sborov, C. and Watson, C. J. Studies of urobilinogen. IV. The quantitative determination of urobilinogen by means of the Evelyn photoelectric colorimeter. *Am. J. Clin. Path.*, 14: 598–604, 1944.
11. Miller, E. B., Singer, K. and Dameshek, W. Use of the daily fecal output of urobilinogen and the hemolytic index in the measurement of hemolysis. *Arch. Int. Med.*, 70: 722–737, 1942.
12. Young, L. E., Platzer, R. F. and Rafferty, J. A. Differential agglutination of human erythrocytes. *J. Lab. & Clin. Med.*, 32: 289–501, 1947.
13. Ervin, D. M., Christian, R. M. and Young, L. E. Dangerous universal donors. II. Further observations on *in vivo* and *in vitro* behavior of isoantibodies of immune type present in group O blood. *Blood*, 5: 552–565, 1950.
14. Young, L. E., Izzo, M. J. and Platzer, R. F. Hereditary spherocytosis. I. Clinical, hematologic and genetic features in twenty-eight cases with particular reference to the osmotic and mechanical fragility of incubated erythrocytes. *Blood*, in press.
15. Shen, S. C., Ham, T. H. and Fleming, E. M. Studies on destruction of red blood cells. III. Mechanisms and complications of hemoglobinuria in patients with thermal burns: spherocytosis and increased

osmotic fragility of erythrocytes. *New England J. Med.*, 229: 701–713, 1943.

16. Shen, S. C., Castle, W. B. and Fleming, E. M. Experimental and clinical observations on increased mechanical fragility of erythrocytes. *Science*, 100: 387–389, 1944.
17. Christian, R. M., Miller, G. and Young, L. E. Unpublished observations.
18. Dacie, J. V. and de Gruchy, G. C. Auto-antibodies in acquired haemolytic anaemia: with particular reference to the use of trypsinized red cells and the red cells from patients with paroxysmal nocturnal hemoglobinuria in the detection of haemolysins. *J. Clin. Path.*, in press.
19. Russ, E. M., Luckey, E. H. and Reader, G. G Cryoglobulinemia. II. Chemical characteristics of a cold precipitable protein obtained in a case of multiple myeloma. To be published.
20. Elkington, J. R. and Winkler, A. E. Transfers of intracellular potassium in experimental dehydration. *J. Clin. Investigation*, 23: 93–101, 1944.
21. Evans, R. S. and Duane, R. T. Acquired hemolytic anemia. I. The relation of erythrocyte antibody production to activity of the disease. II. The significance of thrombocytopenia and leukopenia. *Blood*, 4: 1196–1213, 1949.
22. Young, L. E., Platzer, R. F., Ervin, D. M. and Izzo, M. J. Hereditary spherocytosis. II. Observations on the role of the spleen. *Blood*, in press.
23. Doan, C. A., Wright, C. S., Wheeler, W. E., Bouroncle, B. A., Houghton, B. C. and Dodd, M. C. Some cyto-immunologic aspects of the hypersplenic syndromes. *Tr. Am. A. Physicians*, 63: 172–182, 1950.
24. Castle, W. B., Ham, T. H. and Shen, S. C. Observations on the mechanism of hemolytic transfusion reactions occurring without demonstrable hemolysin. *Tr. Am. A. Physicians*, 63: 161–171, 1950.
25. Valentine, W. N., Craddock, C. G. and Lawrence, J. S. Relation of adrenal cortical hormone to lymphoid tissue and lymphocytes. *Blood*, 3: 729–754, 1948.
26. Craddock, C. G., Valentine, W. N. and Lawrence, J. S. The lymphocyte: studies on its relationship to immunologic processes in the cat. *J. Lab. & Clin. Med.*, 34: 158–177, 1949.
27. White, A. Relation of the adrenals to immunity *Bull. New York Acad. Med.*, 24: 26–31, 1948.
28. Fischel, E. E. The relationship of adrenal cortical activity to immune responses. *Bull. New York Acad. Med.*, 26: 255–260, 1950.
29. Spain, D. M., Malomut, N. and Haber, A. Biological studies on cortisone in mice. *Science*, 112: 335, 1950.
30. Forsham, P. H., Thorn, G. W., Prunty, F. T. G. and Hills, A. G. Clinical studies with pituitary adrenocorticotrophin. *J. Clin. Endocrinol.*, 8: 15–66, 1948.
31. Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F. Observations on the physiologic effects of cortisone and ACTH in man. *Arch. Int. Med.*, 85: 199–258, 1950.
32. Bartter, F. C., Fourman, P., Albright, F., Forbes, A. P., Jefferies, W. M., Griswold, G., Dempsey, E., Bryant, D. and Carroll, E. The effect of adrenocorticotrophic hormone in panhypopituitarism. *J. Clin. Investigation*, 29: 950–971, 1950.

Coarctation of the Aorta in Infancy

Report of Two Cases with Death from Left Ventricular Failure

H. MILTON ROGERS, M.D., COUNCILL C. RUDOLPH, M.D. *and* JOHN H. CORDES, JR., M.D.
St. Petersburg, Florida

THE clinical manifestations of coarctation of the aorta occurring in infancy differ greatly from the picture produced by the same anomaly in adult life. While Abbott[1] stimulated much interest in coarctation of the aorta in adults, she stated that in infants the anomaly was of little importance because it usually existed with other grave congenital cardiac anomalies. However, coarctation of the aorta may be the sole cause of cardiac failure in infants and its recognition is a matter of more than academic interest. The establishment of early diagnosis of aortic coarctation is of even greater importance since surgical measures may effect a cure in these cases, even in infancy.

Calodeny and Carson[2] in 1950 reported twenty-two cases of coarctation of the aorta observed in infancy. These authors emphasized that one of the most common causes of cardiac failure in infants less than two months of age is coarctation of the aorta. In their series of cases of coarctation of the aorta other severe congenital abnormalities of the heart and great vessels were noted in 27 per cent of the cases. Gross[3] likewise commented on cardiac failure occurring in babies as a result of aortic block. This author observed eight babies with cardiac enlargement and failure developing within the first year of life as a result of coarctation of the aorta. Bahn, Edwards and DuShane[4] have observed three infants who died of left ventricular failure as a result of coarctation of the aorta with poorly developed collateral circulations.

In the two cases recorded herein, left ventricular failure occurred at an early age; in one case supraventricular tachycardia was also present. In the second case certain clinical observations made the diagnosis of coarctation of the aorta difficult and led to the erroneous diagnosis of congenital intracardiac disease.

CASE REPORTS

CASE I. *Coarctation of the aorta associated with supraventricular tachycardia.* The patient was a male infant born on June 5, 1950. Physical examination at birth failed to reveal any abnormality. Nine days after birth dyspnea was observed after feeding. On the next day dyspnea became more pronounced and supraventricular tachycardia was observed. (Fig. 1.) No record was made as to the condition of the femoral pulses. The physical examination now revealed an acutely ill infant. The apical rate of the heart was approximately 200 beats per minute, and the respiratory rate was approximately 100 per minute. Auscultation of the heart revealed a gallop rhythm. In spite of digitalization, oxygen and supportive treatment, death occurred on June 16, 1950, at the age of eleven days.

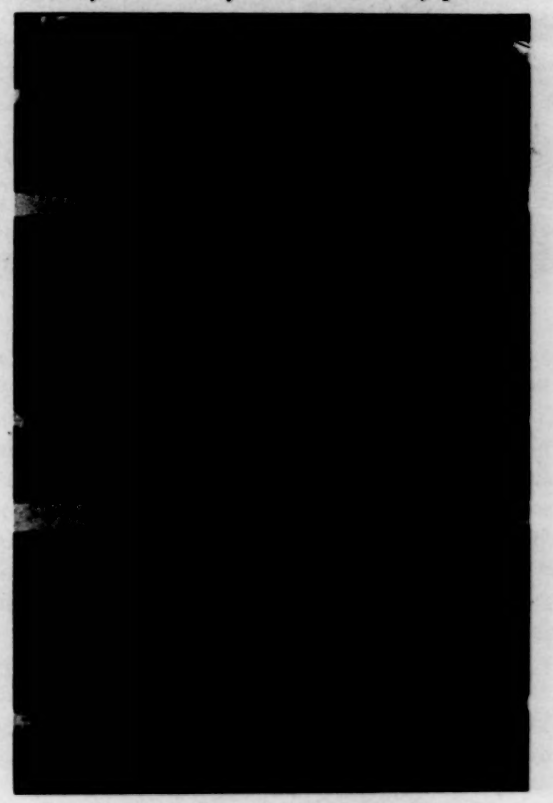


FIG. 1. Case I. Supraventricular tachycardia.

At necropsy the pertinent findings were confined to the heart and great vessels. The heart

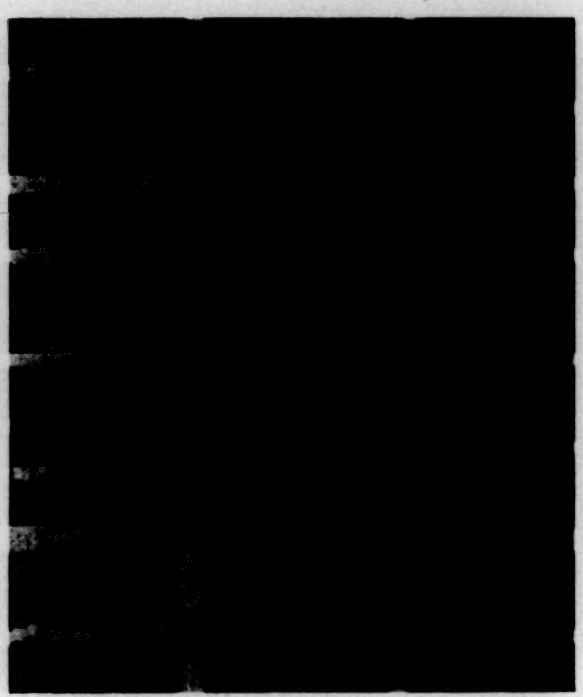


FIG. 2. Case II. Right heart strain.

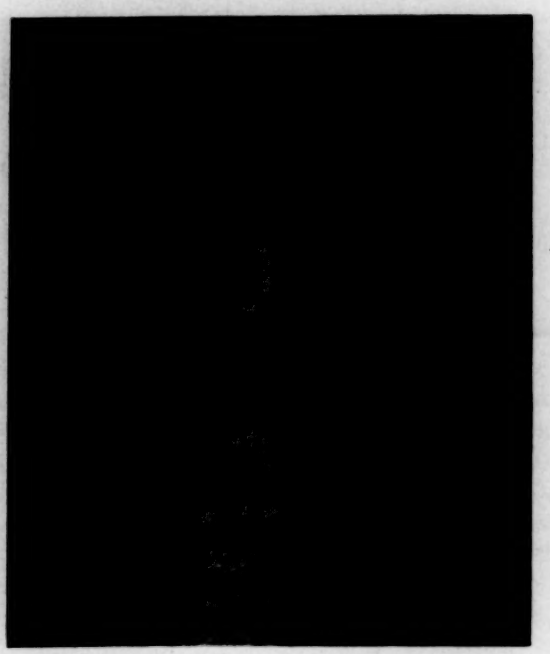


FIG. 3. Case II. Marked cardiac enlargement.

weighed 23 gm. The ventricular septum was intact. The aorta revealed coarctation for a distance of 3.0 mm., originating distal to the left subclavian artery and proximal to the ductus arteriosus. At this point the lumen of the aorta measured 1.0 mm. in diameter, while on either side of the coarctation it measured 3.0 mm. in diameter. The ductus arteriosus, which arose from the left pulmonary artery, was widely patent and measured 3.0 mm. in diameter.

CASE II. *Coarctation of the aorta with left ventricular failure:* The patient was a white male infant born on June 4, 1951. He was first examined by one of us (C. C. R.) on June 15, 1951, because of shortness of breath.

The infant was a full-term baby who after delivery had an uneventful week in the nursery. There was no history of cyanosis at birth. The mother noticed, however, that the baby was breathing heavily and the respirations were jerky when she and the baby arrived home on the seventh day postpartum. This shortness of breath became progressively worse. It was accompanied by several choking attacks which were associated with cyanosis.

The physical examination revealed an acutely ill infant with marked respiratory distress. The breathing was rapid, shallow and labored. The eyes, ears, nose and throat were normal. The pupils were equal and reacted to light. Examination of the heart revealed the pulse to be rapid at a rate of 120 beats per minute. The rhythm was regular. No murmurs were heard. The lungs revealed harsh breath sounds bilaterally. There were rales present over both lungs, particularly over the lower lobe on the right side. Examination of the abdomen revealed no enlargement of the liver or spleen. The extremities were normal. There was no clubbing of the digits. The radial pulse could be palpated distinctly. The femoral pulsations were absent, as were the posterior tibial arterial pulsations. The systolic brachial blood pressure was recorded as 150 mm. of mercury.

The following laboratory work was done: The erythrocytes numbered 4,750,000 per cu. mm. of blood. The hemoglobin determination was 14.5 gm. per 100 cc. of blood or 100 per cent. The mean corpuscular hemoglobin was 30 μg. Leukocytes numbered 18,600 per cu. mm. of blood, with 65 per cent polymorphonuclear leukocytes, 7 per cent non-segmented polymorphonuclear leukocytes, 1 per cent metamyelocytes and 27 per cent lymphocytes.

Electrocardiographic examination (Fig. 2) revealed well marked right axis deviation. T-1 was inverted and the T waves were isoelectric in T-2 and T-3 and in all of the V leads. Roentgenographic examination of the thorax revealed marked cardiac enlargement (Fig. 3), particularly to the left. There was passive congestion

of both lungs, most noticeable in the lower lobe of the right lung.

In view of the elevated leukocyte count penicillin therapy was instituted. Digitalization was started, ¼ gr. (about 0.016 gm.) of digitalis being given every four hours for three doses and then every six hours. On digitalization and administration of oxygen the child responded very satisfactorily and was dismissed from the hospital on June 21st, six days after admission.

The child's condition was satisfactory until July 13th at which time he was readmitted to Mound Park Hospital in a state of congestive cardiac failure. There had been a recent respiratory infection. The results of physical examination at this time were unchanged over the previous examination, except for evidence of bronchopneumonia in the right upper lobe. Death occurred in the afternoon of admission.

At necropsy the pertinent findings were confined to the heart and great vessels. The ventricular septum was intact. The foramen ovale was anatomically patent. The aorta revealed coarctation at a point distal to the left subclavian artery and proximal to the ductus arteriosus. The ductus arteriosus, which arose from the left pulmonary artery, was closing and admitted only a very fine probe. (Fig. 4.) The aortic valve was bicuspid. The heart weighed 45 gm. (estimated normal, 20 gm.). The right ventricle measured 8 mm. in thickness and the left 9 mm. The diameter of the ascending aorta was 7.5 mm., of the aortic arch, 5.0 mm., of the aortic lumen at the coarctation, 1.0 mm. and of the descending thoracic aorta, 6.5 mm.

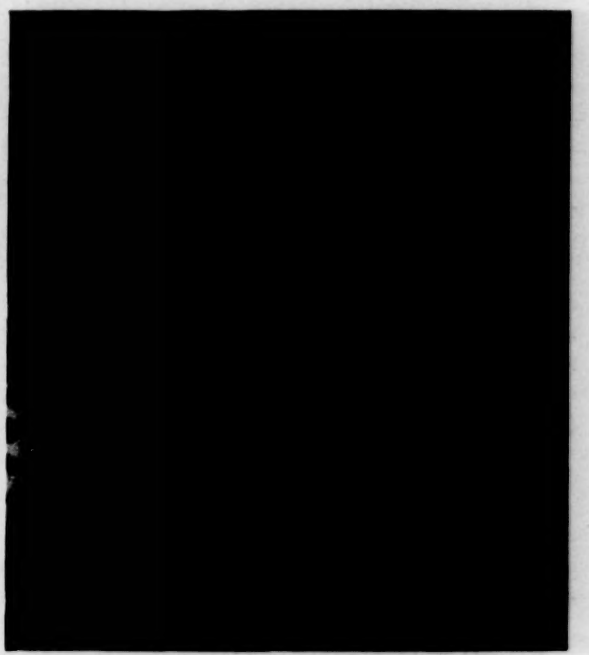


FIG. 4. Case II. The thoracic aorta; the arch appears in the upper part of the photograph, the descending aorta in the lower. The probe extends from the lumen of the closing ductus arteriosus into the aortic lumen. Just proximal to the ductus is the aortic coarctation represented by characteristic infolding of the superior wall of the aorta.

COMMENT

In the first case recorded herein the important clinical manifestations included supraventricular tachycardia and left ventricular failure. The diagnosis of coarctation of the aorta was not suspected clinically. In Case II the possibility of coarctation of the aorta was suspected by one of us (C. C. R.) because of the absence of femoral pulsations and the presence of hypertension of the arms. However, in this case other clinical evidence suggested an intracardiac congenital anomaly. There was well marked right axis deviation. Marked cardiac enlargement was observed by roentgenographic examination. This was predominantly left ventricular enlargement, but enlargement of the cardiac silhouette was observed in the region of the right ventricle and left atrium. These findings suggested the erroneous clinical diagnosis of mitral atresia.

The association of left ventricular failure with evidence of right ventricular hypertrophy in infants should provide a clue to the clinical diagnosis in cases of coarctation of the aorta in early life. In the second case reported herein there was marked cardiac enlargement, including right ventricular dilatation, right axis deviation on the electrocardiogram and right ventricular hypertrophy at necropsy. Evidence of right ventricular enlargement is the result of the requirements of the right ventricle to function as a systemic ventricle in the presence of coarctation proximal to the ductus arteriosus.

The location of the area of coarctation in relation to the ductus arteriosus and its importance as to collateral circulation have been previously emphasized by Bahn, Edwards and DuShane.[4] In our two cases the area of coarctation was proximal to the ductus arteriosus. In accordance with those cases recorded by Bahn and associates, when coarctation of the aorta occurs proximal to the ductus arteriosus, adequate collateral circulation does not develop in fetal life.

The importance of examination of the femoral pulsation in the establishment of an early diagnosis of coarctation of the aorta in infancy should be re-emphasized. In Case II the absence of femoral pulsations suggested the correct diagnosis. The roentgenographic examination of the thorax in cases of coarctation of the aorta in infants may be misleading since marked cardiac enlargement may suggest an intracardiac lesion rather than coarctation of the aorta. Disturbances of cardiac rhythm and conduction may be associated with the coarctation of the aorta in infancy; this occurred in Case I.

SUMMARY

Two cases of coarctation of the aorta occurring in infancy are reported. Left ventricular failure and death occurred in both at an early age. Diagnosis of this anomaly depends on recognition that it produces heart failure at an early age and that pulsations in the femoral artery may be absent. Confusion with congenital intracardiac lesions may result if reliance is placed entirely on electrocardiographic and roentgenographic examination.

REFERENCES

1. Abbott, Maude E. Coarctation of the aorta of the adult type. II. A statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch. *Am. Heart J.*, 3: 392–421, 1928.
2. Calodney, M. M. and Carson, M. J. Coarctation of the aorta in early infancy. *J. Pediat.*, 37: 46–77, 1950.
3. Gross, R. E. Coarctation of the aorta: surgical treatment of one hundred cases. *Circulation*, 1: 41, 1950.
4. Bahn, R. C., Edwards, J. E. and DuShane, J. W. Coarctation of the aorta as a cause of death in early infancy. *Pediatrics*, 8: 192–203, 1951.

Inspiratory-Expiratory Vital Capacity Test of Pulmonary Function*

ALAN LESLIE, M.D.

with the Technical Assistance of Mary E. Leach, R.N.

Los Angeles, California

In the past two decades a number of rather elaborate and complex methods have been evolved for the testing of pulmonary function.[1] These methods have supplemented rather than replaced the simple vital capacity determination, which has, in general, come to be regarded as a test of limited importance. It is the purpose of this paper to present a simple, modified technic of vital capacity testing which can be performed without special laboratory equipment and gives considerable information about pulmonary function not available from the standard expiratory vital capacity procedure.

Christie[2] in 1932 observed that the earliest sign of impaired pulmonary elasticity is a discrepancy between (1) the sum of the complemental and reserve air figures and (2) the vital capacity, as determined in the usual manner, i.e., maximal expiration from the position of maximal inspiration. These two quantities are equivalent in normal subjects, but in patients with hypertrophic emphysema or other pulmonary conditions associated with impaired expiration the former figure is larger than the latter, since impaired pulmonary elasticity or temporary "air-trapping" behind constricted bronchioles interferes with lung emptying but does not impede filling.

Cournand, Richards and Darling,[3] in presenting a method of recording respiratory patterns graphically, recommended the separate recording of the expiratory vital capacity, maximal reserve air and complemental air. They, too, noted that in normal persons the vital capacity figure was equal to the arithmetic sum of the maximal reserve air and the complemental air whereas in emphysematous subjects the vital capacity appeared less than this sum. This was the result of the patients' inability to blow out their maximal reserve air from a start at full inspiration, being better able to do so from a start at quiet expiration.

Goggio[4] advocated kymographic vital capacity records since emphysematous individuals, although occasionally able to expel a normal amount of air, may require an abnormally long time to do this. These patients will produce a curve of slow emptying in contrast to the normal sharp descent, which is symmetrical with the sharp inspiratory rise.

TECHNIC

The subject is connected to a recording ventilometer† of 9 L. capacity approximately half filled with oxygen. After a period of quiet respiration the subject exhales maximally (to point E, Fig. 1), then inhales maximally (to point I, Fig. 1), and immediately exhales maximally (to point E′, Fig. 1). He then breathes normally and, at the option of the observer, may perform any other ventilometric maneuvers desired. EI represents the inspiratory vital capacity and IE′ the expiratory vital capacity.

RESULTS

In all of twenty-five normal adult subjects IE′ was virtually a mirror image of EI, indicating that expiration was no more labored than inspiration. (Fig. 1A.) In five of these subjects EI and IE′ were exactly equal. In nine subjects EI was greater than IE′ in amounts ranging from 10 to 40 cc., or from 0.4 to 1.6 per cent of the vital capacity. This range of variation was not considered significant. In eleven subjects IE′ exceeded EI in amounts ranging from 10 to 160 cc., or from 0.4 to 4.4 per cent of the vital capacity, indicating that in these individuals the ability to exhale was actually greater after

† Many basal metabolism testers are adaptable to the performance of this test.

* From the Medical Service, Wadsworth Hospital, Veterans Administration Center, Los Angeles, Calif.

FIG. 1. Inspiration-expiration vital capacity records. Drum rotation is counterclockwise, so tracings read from right to left. Horizontal lines indicate 40 cc. volume intervals. E, maximum expiration from start at normal inspiration. I, maximum inspiration. E′, maximum expiration from start at maximum inspiration. Group A, three normal subjects; Group B four patients with pulmonary emphysema.

TABLE 1
NORMAL SUBJECTS

Subject	E − E′ Difference (cc.)	Vital Capacity (cc.)	$\frac{E - E'}{VC} \times 100$*
1	0	3,560	0
2	−100	3,520	−2.8
3	20	4,320	0.5
4	−80	3,200	−2.5
5	20	2,660	0.8
6	−100	2,940	−3.4
7	10	2,420	0.4
8	40	3,740	1.1
9	−120	2,720	−4.4
10	−40	3,500	−1.1
11	20	4,600	0.4
12	0	4,640	0
13	0	2,840	0
14	−10	2,580	−0.4
15	30	3,580	0.8
16	−60	5,160	−1.2
17	−40	4,600	−0.9
18	−160	5,080	−3.1
19	0	2,600	0
20	40	2,480	1.6
21	20	2,920	0.7
22	40	2,900	1.4
23	−100	3,500	−2.6
24	0	3,760	0
25	−60	2,760	−2.2
Average:	−25.2	3,463	−0.7

* $\frac{E - E'}{VC} \times 100$ represents the ratio of the E − E′ difference to the vital capacity, expressed in per cent.

the higher "take-off" at maximal inspiration than it was after taking off from normal inspiration. (Table I.) When the figures for the entire group were averaged, the E-E′ differences were represented as a negative quantity when IE′ was greater than EI. The average E-E′ difference was then −25.2 cc. or −0.7 per cent of the vital capacity. In calculating the percentages if EI and IE′ were not equal, the larger figure was used as the vital capacity. The normal group included ten younger individuals chosen at random from the hospital staff. The others in the group were individuals with physical disabilities other than pulmonary or cardiac and in the age distribution of the patients with emphysema.

In thirty-four adult patients with varying degrees of pulmonary emphysema EI was generally normal in slope, although usually less than normal in magnitude, but IE′ was not its mirror image. As expected, the impaired expiration characteristic of the disease resulted in an IE′ curve of slow emptying. (Fig. 1B.) In all patients IE′ was smaller than EI in amounts ranging from 40 to 840 cc., or from 2.7 to 41.7 per cent of the vital capacity, averaging 297 cc. or 16.7 per cent. (Table II.) In calculating these percentages EI, the larger figure, was used as the vital capacity figure. There was excellent correlation of the numerical results and the observed clinical disability. The diagnosis of pulmonary emphysema in these patients was accepted after clinical evaluation by three trained internists who considered, among other things, the history, physical findings, x-rays for

lung appearance and diaphragm movement, exercise tolerance, and other possible causes of dyspnea or decreased breath-holding ability.

Fifteen individuals in the same age group with resting or exertional dyspnea due to heart disease in minimal to moderate decompensation were also tested. (Table III.) Thirteen of these showed figures comparable to those of the normal subjects. Patient No. 14 showed a borderline $\frac{E - E'}{VC} \times 100$ of 2.8. The figure for patient No. 15 was 3.8. This was an extremely obese sixty-five year old man, whose dyspnea was probably as much a result of his obesity as of his arteriosclerotic heart disease. The abdominal obesity possibly interfered with normal respiratory excursion leading to the slightly elevated $\frac{E - E'}{VC} \times 100$. No other explanation was apparent. In order to learn whether or not obesity in itself can be a determining factor, four other abdominally obese individuals but without cardiac or pulmonary disease were studied. These subjects showed $\frac{E - E'}{VC} \times 100$ values of 3.9, 7.0, 7.1 and 11.0, respectively, so it seems reasonable to infer that the figure of 3.8 per cent in cardiac patient No. 15 derived from his obesity rather than from his cardiac disease. The slope of IE′ in all of these cases, including cardiac patient No. 15, was entirely normal.

TABLE II
PATIENTS WITH PULMONARY EMPHYSEMA

Subject	E − E′ Difference (cc.)	Vital Capacity (cc.)	$\frac{E - E'}{VC} \times 100$
1	520	1,720	30.2
2	220	2,500	8.8
3	400	2,560	15.6
4	840	2,200	38.2
5	120	2,180	5.5
6	300	2.080	14.4
7	340	1,760	19.3
8	180	1,920	9.4
9	200	2,360	8.5
10	380	2,880	13.2
11	140	1,760	8.0
12	520	2,520	20.6
13	100	1,900	5.3
14	180	2,380	7.6
15	220	2,620	8.4
16	200	2,080	9.6
17	280	2,880	9.7
18	260	1,440	18.1
19	300	2,080	14.4
20	260	1,500	17.3
21	600	1,440	41.7
22	100	3,060	3.3
23	480	2,140	22.9
24	240	1,720	13.9
25	380	2,240	16.9
26	360	1,520	23.7
27	120	2,440	4.9
28	100	2,120	4.7
29	360	2,180	16.5
30	220	2,140	10.3
31	200	2,680	7.5
32	700	1,880	37.2
33	240	3,640	6.6
34	40	1,500	2.7
Average:	297	2,176	16.7

TABLE III
PATIENTS WITH HEART DISEASE

Subject	E − E′ Difference (cc.)	Vital Capacity (cc.)	$\frac{E - E'}{VC} \times 100$
1	−240	2,920	−8.2
2	0	2,480	0
3	0	2,200	0
4	0	3,120	0
5	60	2,200	2.7
6	−120	2,500	−4.8
7	40	2,500	1.6
8	−200	2,200	−9.1
9	0	3,000	0
10	−140	2,880	−4.9
11	−60	2,720	−2.2
12	0	2,800	0
13	-160	3,460	−4.6
14	60	2,120	2.8
15	100	2,620	3.8
Average:	−44	2,648	−1.5

COMMENTS

The inspiratory vital capacity is a direct record of the sum of the expiratory reserve (supplemental) air and the inspiratory reserve (complemental) air. In performing this part of the test the subject has conveniently filled his lungs and is therefore in position to record his conventional expiratory vital capacity. Comparison of the contours and magnitudes of the two lines (EI, IE′) is convenient and informative. If IE′ demonstrates nearly vertical descent and is equal to or greater than EI, obviously there is no interference with expiration. In the normal group studied eight individuals showed IE′ to be smaller than EI, with normal contour. The greatest E-E′ difference was 40 cc. which was 1.6 per cent of the vital capacity. In the emphysema group the smallest E-E′ difference was also 40 cc. but this proved to be 2.7 per cent of the vital capacity. Furthermore, this patient showed an abnormal IE′ curve of slow emptying. (Fig. 1B, first tracing.)

In studies of this nature borderline cases are to be found in both normal and abnormal groups. It may be of significance, however, to point out that in the present study there was no overlap of $\frac{E - E' \times 100}{VC}$ in the two groups. The demarcation would appear to fall at about 2 per cent. Borderline cases can be further and probably conclusively evaluated if the contour of IE′ is observed, a sharp descent indicating normal expiration, a curve of slow descent indicating impaired expiration. An IE′ of sharp descent with an appreciable E − E′ difference has not been encountered. Neither has there been encountered an IE′ of slow descent of greater magnitude than EI. If these situations should occur, they would have to be individually evaluated. Since patients with impaired pulmonary function are seldom obese, the question of discounting elevated values for $\frac{E-E'}{VC} \times 100$ because of obesity should rarely arise. If, however, just such a case should be encountered, it would also require individual evaluation.

This simple method of dual vital capacity determination may be extended to be more informative. In the group of patients under consideration there may be considerable variation of functional state as a result of weather, psychic factors, infection, etc., with their well known effects on the bronchial musculature. This variability may be quantitated by comparing tests made at different times. Asthmatics and other patients with significant bronchospasm show the greatest variability in $\frac{E - E'}{VC} \times 100$. Patients with impaired pulmonary function resulting principally from fibrosis show the least variability. Results of therapy can be demonstrated by comparison of before-and-after tests. Similarly, the method is also applicable to the objective clinical evaluation of bronchodilator drugs. Studies of this nature are in progress and will be reported later. Since the study of the cardiac group showed that patients with cardiogenic dyspnea have normal values, the test may be an aid in differentiating cardiac and respiratory dyspnea, or in quantitating the relative importance of cardiac and respiratory factors in combined disease.

Since this test can be performed without undue exertion by the patient, it may offer a more accurate clinical index of pulmonary dysfunction in severely ill patients than the maximum breathing capacity. Performance of this latter test requires a great deal of patient effort and cooperation, perhaps more than the severely decompensated subject can or will exert. It is suggested that such patients make excessively poor showings, giving an exaggerated representation of disability. With therapy such patients will be much better able to participate in such a test, as well as more cooperative with the physician-benefactor conducting the test. When such tests are compared, the indicated improvement may then be disproportionately greater than the actual clinical improvement. It has been observed that patients too breathless to perform the maximum breathing capacity test can still produce a satisfactory inspiratory-expiratory vital capacity record. Although, in contrast to the maximum breathing capacity, the dual vital capacity record does not provide an over-all clinical index of pulmonary function, it does demonstrate directly and quantitatively the patient's inability at any given moment to empty his lungs, a principal consideration in lung disease characterized by loss of elasticity or bronchiolar narrowing. When serial tests are compared good clinical correlation is observed.[5] As indicated above, the test is not exhausting so repeated observations may be made at short intervals, as in the evaluation of bronchodilator agents.

SUMMARY

1. A modified technic of vital capacity testing is described. This test can be performed without undue exertion by severely ill patients. It provides information about pulmonary function not available from the conventional expiratory vital capacity procedure, and closely reflects the clinical condition of patients with impairment of expiration. It is a simple test for clinical use and not an elaborate laboratory procedure.

2. The results of tests on thirty-four patients with pulmonary emphysema, twenty-five normal subjects, fifteen patients with heart disease and four obese individuals are presented.

REFERENCES

1. Comroe, J. H., Jr. Methods in Medical Research, vol. 2, pp. 74–244. Chicago, 1950. Year Book Publishers.
2. Christie, R. V. The lung volume and its subdivisions. *J. Clin. Investigation*, 11: 1099, 1932.
3. Cournand, A., Richards, D. W., Jr. and Darling, R. C. Graphic tracings of respiration in study of pulmonary disease. *Am. Rev. Tuberc.*, 40: 487, 1939.
4. Goggio, A. F. The abnormal physiology of chronic pulmonary emphysema. *New England J. Med.*, 231: 672, 1944.
5. Leslie, A. Unpublished observations.

AUTHOR INDEX VOLUME XIII

Abarbanel, A. R., 90
Abildskov, J. A., 104
Adams, J. E., 496
Aggeler, P. M., 90
Aikawa, J. K., 640, 653
Akeroyd, J. H., 273
Aldrich, R. A., 92
Alexander, B., 255
Anderson, A., 109
Anderson, C. T., 496
Arends, T., 650
Aronsohn, R. B., 109
Artman, E. L., 110
Atlas, D. H., 384

Bachman, D. M., 102
Backman, H., 101
Baehr, G., 517, 570, 591
Bakst, H., 235
Barondess, J. A., 294
Barr, D. P., 665
Bartlett, G. R., 90
Barton, W. B., 641
Bassett, S. H., 93
Bates, G., 90
Battey, L. L., 105
Bauer, F. K., 502
Baxter, P., 497, 504
Beck, W. S., 100
Beer, E., 542
Bell, D. M., 641
Belle, M. S., 106
Bellet, S., 145
Bennett, I. L., Jr., 105
Bennett, L. L., 91
Bennett, V. D., 643
Bennett, W. A., 374
Bentinck, R. C., 91
Berenson, G. S., 641
Berg, A. A., 575
Berlin, N. I., 502
Bertino, J., 497, 504, 506
Bierman, H. R., 91, 501, 504, 506
Bishop, J., 497, 504
Blachly, P. H., 102
Blackburn, I., 106, 651
Boling, L., 96, 497, 504
Bondy, P. K., 642
Bongiovanni, A. M., 27
Borges, F., 653
Borges, W., 311
Bosma, J. F., 91
Boyd, R. I., 499
Bramham, J. C., 501
Brill, N. E., 533, 570
Brody, D. A., 73
Brooks, F. S., 501
Brown, E., 502
Brown, H., 92
Bruyn, H. B., 501
Buerger, L., 526
Burch, G. E., 104, 641
Burch, M. S., 104
Burnett, C. H., 107, 651
Burns, T., 641
Burns, T. W., 94, 643
Byers, S. O., 99
Byron, R. L., Jr., 91, 501, 504

Cape, R. D. T., 496
Carnes, H. E., 108
Carr, J., 500
Carruthers, E. P., 496
Cartwright, G. E., 95
Cary, F. H., 105
Cattell, McK., 124
Cayer, D., 653
Chalmers, T. C., 713
Chapman, D. W., 642
Chaudhuri, S. N., 107
Chiamori, C. Y., 102
Christian, E. R., 689
Code, C. F., 328
Cohen, J. E., 643
Commons, R. R., 496, 499, 506
Conley, C. L., 1, 284
Conrad, J. P., 501
Cooley, D. A., 642
Cooper, M., 105
Cooper, T., 374
Cordes, F., 501, 504
Cordes, J. H., Jr., 805
Cotter, T. P., 713
Craig, A. B., 793
Crispell, K. R., 247
Crohn, B. B., 583
Cronvich, J. A., 104
Crosby, W. H., 273
Culiner, M., 97

Dameshek, W., 35
Daniels, D. D., 502
David, N. A., 99
Davison, K. B., 92
Dawson, N., 96, 506
DeLaney, R., 97
Deschamps, S. H., 674
DeWind, L. T., 499
DiCaprio, J. M., 98
Dobriner, K., 432
Doolan, P. D., 104
Doyle, J. T., 642
Drury, D. R., 101
Dubois, E. L., 496
Duke, T. W., 645

Eagle, H., 389
Ebeling, W. C., 643
Eckhardt, G. C., 498
Eddy, B., 506
Eiler, J. J., 506
Eisemann, G., 21
Eisenberg, B., 640
Eisenberg, E., 496
Eisenmenger, W. J., 27
Ely, R. S., 96
Engel, F. L., 643
Englert, E., Jr., 507
Epstein, A. A., 556
Ethridge, C. B., 704
Evans, J. D., 105
Evans, J. M., 704
Evans, R. S., 500

Faloon, W. W., 12
Felts, J. H., 640
Fieber, M. H., 725
Finch, C. A., 92
Finnerty, F. A., Jr., 643
Fitzhugh, F. W., Jr., 644
Flowe, B. H., 645
Fluss, H. R., 502, 503
Foley, W. T., 103
Follette, J. H., 100
Folley, J. H., 311
Foraker, A. G., 108
Frankel, R. A., 108
Freedman, M., 110
Freedman, R. I., 93
Freis, E. D., 103, 644
French, A. B., 93
Friedman, M., 99
Fukayama, G., 96
Furman, E., 653
Futch, E. D., 423

Gabrio, B. W., 92
Galdston, M., 432
Gellhorn, A., 428
Gendel, B. R., 3
Gilfillan, R., 91
Ginsburg, B., 93
Ginzburg, L., 583
Glendening, M. B., 90

Author Index

Gluck, J., 124
Gofman, J. W., 500
Gold, H., 124
Goldman, R., 93
Goldstein, R., 255
Gordan, G. S., 496
Gray, F. G., 400
Green, H. D., 644, 647, 650
Green, T. W., 284
Greene, R. W., 12
Greer, R., 96, 506
Gregory, L., Jr., 423
Greig, M. E., 646
Greiner, T., 124
Grimson, K. S., 645
Gunnison, J. B., 95
Gutman, A. B., 744
Guyton, A. C., 645

Hagan, R. C., 643
Hahn, E. O., 498
Halstead, J., 505
Handley, C. A., 103
Harper, H., 496
Harper, H. A., 94
Harrell, G. T., 640
Hartmann, R. C., 284
Hecht, H. H., 101, 498
Heller, C. G., 98
Henstell, H. H., 93
Hershorn, S. E., 713
Hess, W. C., 647
Heyman, A., 105, 645
Hickam, J. B., 106, 652
Higgins, A. R., 94
Higgins, T. F., 103
Hightower, H. A., 653
Hightower, N. C., Jr.. 328
Hirsch, J., 108
Hirsh, S. A., 145
Hoagland, R. J., 158
Hobson, Q. J. G., 496
Hoch-Ligeti, C., 646
Hoffbauer, F. W., 109
Hogness, J. R., 94
Holland, W. C., 646
Hollander, F., 453
Holley, H. L., 107
Holman, E., 95
Hopper, J., Jr., 502, 503
Howell, D. A., 641
Hrenoff, M., 506
Hudson, D., 124
Huie, R. A., 644
Hultgren, H., 95, 503
Huntington, R. W., 497
Hurst, W. W., 503
Hyde, G. M., 502

Israel, H. L., 413

Jackson, C. E., 104
Jaffe, I., 428
James, G. W., 109
Janowitz, H. D., 465
Jawetz, E., 95
Jayne, H. W., 106, 651
Jeghers, H. J., 104
Jensen, W. N., 95
Johnson, I. T., 642
Johnson, R. L., 644
Joiner, E. E., 668
Jones, H. B., 500
Jones, R. E., 94

Kaine, H. D., 505
Kamenear, H., 384
Kaplan, L., 505
Kelley, R. T., 103
Kelley, V. C., 96
Kelly, K. H., 91, 501, 504
Kempe, C. H., 500
Kenoyer, W. I., 108
Kerby, G. P., 646
Kester, N. C., 647
Kibler, R. F., 647
Kimbrough, J. E., 107
Kimmel, J. R., 94
Kinsell, L. W., 96, 97, 497, 499, 504, 506
Kirsner, J. B., 615
Klein, C. L., 94
Klemperer, P., 591
Kligerman, M. M., 428
Knowlton, A. I., 597
Kory, R. C., 104
Kramer, M., 124
Kraus, A. P., 3
Krevans, J. R., 284
Kwit, N., 124
Kyle, L. H., 104, 647

LaBoccetta, A. C., 413
LaDue, J. S., 110
Lange, J., 97
Lange, J. D., 502
Larson, R. K., 497
Lauster, C. F., 111
Leake, T. B., 90
Lee, N. D., 97
Leeds, S. E., 97
Legerton, C. W., Jr., 648
Leibowitz, S., 172, 235
Lealie, A., 809
Levin, W. C., 108
Lewis, L., 497, 504
Lewisohn, R., 550
Libman, E., 544
Liddle, G. W., 91
Lightfoot, R. M., 107
Littman, S. M., 504
Liu, C. K., 500
Lozner, E. L., 12

Machella, T. E., 760
Madison, L., 652
Mandel, E. E., 322
March, H. W., 46
Margen, S., 96, 97, 497, 504, 506
Marlow, A. A., 90
Maroney, M., 98
Marsh, R., 124
Martin, S. P., 107
Masouredis, S. P., 501
Mathes, S., 124
McDevitt, E., 103
McIntosh, H. W., 496
Meneely, G. R., 104
Merrill, A. J., 644
Meyer, A., 497, 504
Meyer, L. M., 502
Michaels, G. D., 96, 499
Miller, S. I., 649
Mills, H., 100
Mills, L. C., 103, 642, 648
Mitchell, G. L., Jr., 105
Modell, W., 124
Molander, D. W., 110
Molle, W. E., 505
Morkovin, D., 58
Morlock, C. G., 328
Mortimore, G. E., 98
Moschcowitz, E., 519, 567
Moyer, J. H., 103, 648, 649
Muirhead, E. E., 649
Myers, J. D., 647, 649, 653

Nabatoff, R. A., 242
Nelson, D. H., 96, 98
Newkirk, J., 497, 504
Nishahara, H., 102

O'Connell, B. P., 502, 503
Olney, M. B., 501
Oppenheimer, G. D., 583
Otto, H., 124

Page, E., 90
Palmer, J. G., 98
Palmer, R. A., 496
Palmer, W. L., 615
Parker, R. T., 643, 653
Parson, W., 247
Parsons, R. J., 502
Partridge, J., 497, 504
Partridge, J. W., 96, 505
Patterson, J. L., Jr., 105, 645, 650
Paulsen, C. A., 98
Pease, G. L., 374
Perri, A. M., 413
Petrakis, N. L., 501

Author Index

Plotz, C. M., 597
Prentice, T. C., 668
Prinzmetal, M., 121
Purdy, A., 95

Quigley, J. P., 73
Quinn, J. P., 400
Quinn, R. W., 400

Ragan, C., 597
Raile, R. B., 96
Rantz, L. A., 98
Rather, L. J., 499
Ratnoff, O. D., 111
Rich, M., 106, 651
Richardson, A. W., 647, 650
Ritvo, M., 713
Roberts, G., 650
Robertson, D., 124
Robinson, H. S., 496
Roehm, D. C., 104
Rogers, H. M., 805
Rosenman, R. H., 99
Rosenthal, N., 570
Rowan, R., 505
Rowe, C. R., Jr., 645
Rubin, I. C., 562
Rudolph, C. C., 805
Ruffin, J. M., 648
Rundles, R. W., 641, 650
Ryan, J. M., 106

Saifer, A., 730
Sandberg, A. A., 98, 498
Scheinberg, P., 106, 651
Schemm, F. R., 503
Schieve, J. F., 105, 641
Schifrin, A., 591
Schilling, M. O., 111
Schlyen, S. M., 46
Schnaper, H. W., 644
Schroeder, H. A., 651
Schwartz, S. E., 46
Seaman, A. J., 99
Seavey, P. W., 650
Seldin, D. S., 107, 651
Selzer, A., 95
Semler, J. J., 99
Sensenbach, W., 652
Sholl, J. G., 111
Sieker, H. O., 652
Sigel, M. M., 413
Silver, H. K., 500
Silver, S., 725
Simkin, F., 100
Siri, W., 668
Sirota, J. H., 242
Skaggs, R. H., 642
Skelton, J., 648
Slater, R. J., 27
Smith, T. W. D., 94
Smyrl, S., 96
Smyth, F. S., 500
Snapper, I., 655
Snyder, H., 649
Spaet, T. H., 35
Starr, P., 100, 496
Stead, E. A., Jr., 387
Steele, J. M., 432
Steer, A., 674
Stein, C. S., Jr., 506
Stephens, G., 497, 504
Stetten, D., Jr., 251
Stevens, A. R., 92
Stickney, J. M., 374
Stone, C. T., 108, 423
Stone, R., 497, 504
Stowens, D., 498
Strait, L. A., 506
Stueck, G. H., Jr., 183

Tarver, H., 97
Tashnek, A. B., 649
Taylor, F. W., 108
Taylor, W. J., 647, 649, 653
Texter, E. C., Jr., 648
Thomas, L. E. J., 704
Tivey, H., 500
Tulloch, J., 103
Tunis, M., 103
Tyler, F. H., 98, 498
Tyor, M. P., 653

Valentine, W. N., 100

Walser, M., 107, 651
Walsh, W. P., 104, 647
Warren, J. V., 642
Warshaw, L., 124, 507
Waterhouse, C., 793
Weiner, H. A., 58
Wells, B. B., 654
White, F. W., 713
White, L., 91, 501, 504
White, S. G., 90
Whittington, B., 502
Wick, A. N., 101
Wilkerson, V., 109
Wilkinson, E. L., 101
Williams, R. H., 94, 97
Williams, W. L., 109
Wilmer, J. G., 704
Wilson, J. S., 642
Wilson, S. J., 21
Wilson, W. P., 105
Winkler, R., 497, 504
Wintrobe, M. M., 95
Winzler, R. J., 102
Wise, R. A., 110
Workman, J. B., 653
Wortham, J. T., 654
Wright, I. S., 103

Yamawaki, T., 311
Yeomans, A., 183
Yin Tang Hsu, 646
Yohalem, S. B., 725
Youmans, W. B., 102, 209
Young, J. M., 3
Young, L. E., 793
Yow, E. M., 108, 654
Yü, T. F., 744

Zamcheck, N., 713
Zeeman, S. E., 145
Zimmerman, H. J., 704

SUBJECT INDEX VOLUME XIII

(ab.) = Abstract; (CPC) = Clinico-pathologic Conference; (E.) = Editorial

Absorption tests, differential, in infectious mononucleosis, 172
Abstracts of
  American Federation for Clinical Research
    southern sectional meeting, January 18, 1952, 103
    western sectional meeting, January 24, 1952, 496
  Southern Society for Clinical Research
    annual meeting, January 19, 1952, 640
  Western Society for Clinical Research
    fifth annual meeting, January 25, 1952, 90
Acid-base abnormalities, 183
Acromegaly
  mandibular tumor and pyrexia (CPC), 366
  with hemorrhagic necrosis of pituitary adenoma and hyperthermia (CPC), 366
ACTH
  and acceleration of neoglucogenesis from fat (ab.), 96
  and alkalosis (ab.), 651
  and blood levels (ab.), 98
  and cortisone, effects of, on cerebral circulation (ab.), 652
    potassium loss with (ab.), 640
  and hypercoagulability of blood in hepatic cirrhosis, 27
  and potassium, metabolic interrelationships between (ab), 91
  and renal excretion of chlorides (ab.), 107
  and thrombocytopenia, 12
  cortisone and chemotherapy in meningitis (ab.), 497
    and chemotherapy in peritonitis (ab.), 497
      in tuberculosis (ab.), 504
  effect of, on thrombocytopenic purpura, 21
    various brands of (ab.), 505
  eosinopenic response to (ab.), 496
  in refractory anemia (ab.), 641
Adrenal
  cortex and carbohydrate metabolism (ab.), 643
  steroids and blood levels (ab.), 98
Adrenalectomy, effect of, on TTC reductase activity (ab.), 646
Adrenocortical function in depressed states and alcoholism (ab.), 506
Alcaptonuria and ochronosis, 432
Alimentary canal, motility of, 328
Alkalosis
  and ACTH (ab.), 651
  metabolic, and cerebral blood flow (ab.), 105
American Federation for Clinical Research, abstracts of
  southern sectional meeting, January 18, 1952, 103
  western sectional meeting, January 24, 1952, 496
Amidation of glutamic acid by brain (ab.), 496
Aminophylline in hypertensive headache (ab.), 649
Amphenone "B," effect of, on adrenal and thyroid (ab.), 94
Analgesia and ergot alkaloids (ab.), 99
Anemia
  arterial oxygen pressure in (ab.), 106
  chronic, circulation and metabolism in (ab.), 645
  Cooley's, 46
    and chronic hepatitis, 507
  febrile, pleiochromic (reprint), 567
  hemolytic, hemoglobin synthesis in, 273
  intravenous iron in (ab.), 501
  pernicious, and vitamin B_{12}, 284
  refractory, ACTH in (ab.), 641
Antibiotic synergism and antagonism (ab.), 95
Antibiotics
  and fecal pigments (ab.), 109
  and post-streptococcal electrocardiograms (ab.), 498
  and Pseudomonas aeruginosa (ab.), 654
Antigen-antibody reactions, 352
Antiglobulin serum test by injection of homologous blood (ab.), 500
Anuria and oliguria, serum potassium patterns in (ab.), 503
Aorta
  coarctation of, 805
  thoracic, occlusion of, with mechanical shunt (ab.), 97
Aplastic anemia in a patient receiving chloramphenicol (CPC), 782
Arterial pressure and change in body position (ab.), 650
Arteries, visceral, vasomotor reaction of, to epinephrine (ab.), 91
Ascitic fluid circulation with tritium-labeled water, 668
Atherosclerosis
  diabetic, lipid studies in (ab.), 499
  diet in (E.), 665
Autoimmune hemolytic disease and leukemia, 793

Barbiturate poisoning and hemodialysis (ab.), 104
Bile
  ducts, rupture of echinococcic cysts into, 384
  pigment excretion and hemolytic anemia, 273
Bladder, urinary, removal of neoplasms from (reprint), 542
Blood
  cell, red, glucose metabolism in (ab.), 90
  disorders in disseminated lupus erythematosus (E.), 1
  eosinophils, circulating, in infectious disease, 58
  flow and influence of pH (ab.), 647
    in bone marrow (ab.), 501
  hypercoagulability of, in hepatic cirrhosis, 27
  preserved, storage lesion in (ab.), 92
  radioactivity of, after oral I^{131}, 725
  transfusion by citrate method (reprint), 550
  volume expansion with dextran, gelatin and plasma (ab.), 502

Bone marrow
aspiration and thrombocytopenic purpura, 374
blood flow in (ab.), 501

Cancer, triethylene melamine in, 428
Cardiac
actions in digitalization, 124
output and dye dilution method (ab.), 642
Cardiogenic "shock," mechanism of (ab.), 644
Carotid artery, internal, thrombosis of (ab.), 652
Cell membrane defect in rheumatic fever (ab.), 640
Cerebral
blood flow and metabolism, effects of age on (ab.), 651
circulation and metabolism in sickle cell anemias (ab.), 645
effects of ACTH and cortisone on (ab.), 652
hemodynamic effects of aminophylline in hypertensive headache (ab.), 649
Chloramphenicol in pneumonia (ab.), 643
Chloromycetin in acetyl dimethylamine, effects of (ab.), 108
Cholesterol metabolism in hyper- and hypothyroid states (ab.), 99
Cholinesterase activity and permeability of auricles to sodium and potassium (ab.), 646
Chromogens, urinary in acute porphyria (ab.), 92
Circulation, peripheral, diffuse disease of (reprint), 591
Cirrhosis
hepatic, hypercoagulability of blood in, 27
of liver, diurnal variation in steroid excretion in (ab.), 93
portal, hypokalemia in (ab.), 110
Clinic on psychosomatic problems (Massachusetts Gen'l. Hospital)
Hyperventilation in a patient who stammered, 777
Clinico-pathologic conferences (Washington Univ.)
acromegaly, mandibular tumor and pyrexia, 366
aplastic anemia in a patient receiving chloramphenicol, 782
fever of unknown origin, 82
leukemoid reaction, abdominal pain and mesenteric lesions, 487
progressive visual loss, right-sided weakness and sudden death, 227
Coarctation of aorta in infancy, 805
Cobalt in hypoplasia (ab.), 99
Colitis, ulcerative
liver in (ab.), 505
problems in, 760
Combined staff clinic (Columbia Univ.)
antigen-antibody reactions, 352
Conference on therapy (Cornell Univ.)
treatment of obesity, 478
Cooley's anemia, 46
and chronic hepatitis, 507
Coproporphyrin excretion and body weight (ab.), 506
and acceleration of neoglucogenesis from fat (ab.), 96
and chloramphenicol in Rocky Mountain spotted fever (ab.), 653
Cortisone and renal excretion of chlorides (ab.), 107
and thrombocytopenia, 12
effect of, on thrombocytopenic purpura, 21
in hypoplasia (ab.), 99
Cryoglobulinemia and leukemia, 793
Cushing's syndrome
and hydrocephalus, 247
natural history of, 597

Deficiency of plasma thromboplastin component (ab.), 90
Deglutition, mechanisms of, in bulbar-pharyngeal poliomyelitis (ab.), 91
Desoxyribonuclease, inhibitor of (ab.), 93
Deuterium oxide in edema (ab.), 503
Dextran, blood volume expansion with (ab.), 502
Diet in atherosclerosis (E.), 665
Digestive tract, development of pressures in, 73
Digitalization, cardiac and emetic actions in, 124
Disease, infectious, of unknown origin (reprint), 533
Disseminated lupus erythematosus, redox reaction of leukocytes in (ab.), 107
Dystrophy, muscular, heart in (ab.), 498

Edema
cause of, in nephritis (reprint), 556
deuterium oxide in (ab.), 503
Electrocardiograms, post-streptococcal, and antibiotics (ab.), 498
Emetic actions in digitalization, 124
Endocarditis, bacterial, due to Pseudomonas aeruginosa (ab.), 108
Endocrine factors in heart failure (ab.), 644
Eosinopenia in acute infections, 58
Eosinopenic responses to ACTH (ab.), 496
Epinephrine
intra-arterial, into spleen (ab.), 504
reactions of visceral arteries to (ab.), 91
Ergot alkaloids and potentiation of analgesia (ab.), 99
Etamon, effects of, in peripheral vascular disease (ab.), 644
Ethanol and cerebral blood flow (ab.), 105

Fainting (E.), 387
Fallopian tubes, patency of (reprint), 562
Fever of unknown origin (CPC), 82
Foreword (to Mount Sinai Hospital Anniversary number), 517
Fructolysis index in seminal fluid (ab.), 90
Fructose and sugar, utilization of, in humans (ab.), 506

Gastrectomy, subtotal, for ulcer (reprint), 575
Gastric secretions, physiology of, 453
Gastrointestinal
function, quantitative tests of, 465
tract, neural regulation of motility of, 209

Gelatin, blood volume expansion with (ab.), 502
Globin, modified, human, effects of (ab.), 647
Glucose
  metabolism, action of insulin on (ab.), 101
    in red blood cell (ab.), 90
  output by liver (ab.), 642
Gout, management of, 744

Headache, hypertensive, aminophylline in (ab.), 649
Heart
  disease, effect of exercise on peripheral venous pressure in (ab.), 502
  failure, altered liver function in, 704
    and endocrine factors (ab.), 644
    and hexamethonium (ab.), 103
    diurnal variation in steroid excretion in (ab.), 93
  in muscular dystrophy (ab.), 498
Hemodialysis and barbiturate poisoning (ab.), 104
Hemoglobin synthesis
  in hemolytic anemia, 273
  measurement of (ab.), 95
Hemorrhage
  during pregnancy, 111
  gastrointestinal, and roentgen diagnosis, 713
Hepatitis
  chronic, and Cooley's anemia, 507
  hepatic circulation in (ab.), 653
Heterophil antibodies in infectious mononucleosis, 235
Hexamethonium
  and heart failure (ab.), 103
  and renal hemodynamics (ab.), 103
  in hypertension (ab.), 651
Hydrazinophthalazine in hypertension (ab.), 651
1-Hydrazinophthalazine, cardiovascular and renal adjustments to (ab.), 101
Hydrocephalus and Cushing's syndrome, 247
2-Hydroxystilbamidine in American leishmaniasis, 655
Hyperinsulinism, pancreatic, and pituitary adrenocortical system (ab.), 92
Hyperplasia, adrenal, metabolic studies in (ab.), 96
Hypertension
  pulmonary, and patent ductus arteriosus (ab.), 95
  renal vein, and splenorenal vein anastomosis, 242
Hyperthyroidism, I^{131} uptake in (ab.), 502
Hyperventilation in patient who stammered, 782
Hypofibrinogenemia and the hemorrhaging tendency, 111
Hypokalemia in portal cirrhosis (ab.), 110
Hypoplasia
  cobalt and cortisone in (ab.), 99
  of bone marrow with disseminated moniliasis and hemorrhage into lumen of stomach and intestine (CPC), 782
Hypoxemia, electrocardiographic manifestation of (ab.), 104

I^{131}
  excretion of, in cirrhosis (ab.), 653
  uptake in hyperthyroidism (ab.), 502
Ileitis
  regional (reprint), 583
    liver in (ab.), 505
Infection by hemolytic streptococci in childhood (ab.), 98
Insulin
  action of, on glucose metabolism (ab.), 101
  fixation in femoral artery (ab.), 641
Iron deficiency anemias, intravenous iron in (ab.), 501

Jaundice, obstructive, hepatic circulation in (ab.), 653

Kidney function and splenorenal vein anastomosis, 242

Leishmaniasis, American, mucocutaneous, 655
Leukemia
  chronic, lymphocytic, 793
  in survivors of atomic bomb, 311
  of childhood, prognosis in (ab.), 500
Leukemoid reaction, abdominal pain and mesenteric lesions (CPC), 487
Leukocytes in myeloproliferative syndromes (ab.), 100
Lipid studies in diabetic atherosclerosis (ab.), 499
Lipoproteins of serum in normals and diabetics (ab.), 500
Liver
  biopsies, histochemical studies of (ab.), 109
  disease, operative risk in (ab.), 93
    serum cholinesterase in (ab.), 110
  function, altered, in congestive heart failure, 704
  glucose output by (ab.), 642
  in ulcerative colitis and regional ileitis (ab.), 505
  needle biopsy of, 689
Lupus erythematosus
  blood disorders in (E.), 1
  systemic, treatment of (ab.), 496
Lymph follicle hyperplasia of lymph nodes and spleen (reprint), 570

Malignancy
  photometric analysis of light absorption in (ab.), 108
  serum cholinesterase in (ab.), 110
    triethylene melamine in (ab.), 650
Mediterranean
  anemia and chronic hepatitis, 507
  hemopathic syndromes, 46
Meningitis, ACTH, cortisone and chemotherapy in (ab.), 497
Metabolic response to injury (ab.), 643
Metabolism of radioactive acetate by tubercle bacilli (ab.), 102
Methanol and cerebral blood flow (ab.), 105
Methedrine and psychotherapy, 782
Methyl
  alcohol poisoning (ab.), 105
  androstenediol, metabolic studies with (ab.), 505
Mitral
  stenosis and valvulotomy (ab.), 642
  valvulotomy (ab.), 503

Mononucleosis, infectious, 158, 172, 235
Motility of alimentary canal, 328
Mount Sinai Hospital
  anniversary issue, 517–596
  founding and early days, 519
  reprints in anniversary issue of, 517–596
    a study of the endocardial lesions of subacute bacterial endocarditis, with particular reference to healing or healed lesions, 544
    an acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries, 567
    an acute infectious disease of unknown origin, 533
    blood transfusion by the citrate method, 550
    concerning the causation of edema in chronic parenchymatous nephritis, 556
    diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis, 591
    generalized giant lymph follicle hyperplasias of lymph nodes and spleen, 570
    mortality and late results of subtotal gastrectomy for the radical cure of gastric and duodenal ulcer, 575
    nonoperative determination of patency of fallopian tubes, 562
    regional ileitis, a pathologic and clinical entity, 583
    removal of neoplasms of the urinary bladder: a new method employing high frequency (Oudin) currents through a catheterizing cystoscope, 542
    thrombo-angiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene, 526
Multiple sclerosis with cortisone therapy and pulmonary embolus (CPC), 227
Myasthenia gravis, octamethyl pyrophosphoramide in, 423
Myocardial infarction, alterations in (ab.), 644

Necrosis, renal, medullary, 322
Needle biopsy of liver, 689
  at Hepatitis Center, 674
Neomycin in bacterial endocarditis (ab.), 108
Neoplasms of urinary bladder (reprint), 542
Nephrectomy, renal transplants after (ab.), 649
Nephritis
  cause of edema in (reprint), 556
  glomerular, nitrogen mustard in (ab.), 499
Neural regulation of gastric and intestinal motility, 209
Neutropenia, chronic, hypoplastic, 35
Nitrogen mustard in glomerular nephritis (ab.), 499
Nor-epinephrine and renal hemodynamics (ab.), 648

Obesity, treatment of, 478
Ochronosis and alcaptonuria, 432
Octamethyl pyrophosphoramide in myasthenia gravis, 423
Owren's disease, 255
Oxygen
  consumption, effect of methanol and ethanol on (ab.), 105
  inhalation in chronic anemia (ab.), 645
Oxypolygelatin, a plasma volume expander (ab.), 94

Pancreas, hyperglycemic-glycogenolytic factor of (ab.), 647
Papaverine, intravenous, and cerebral blood flow (ab.), 106
Parahemophilia in three siblings, 255
Patency of Fallopian tubes (reprint), 562
Patent ductus arteriosus and pulmonary hypertension (ab.), 95
Penicillin, treatment failure with, 389
Pericarditis, coccidioidal (ab.), 497
Peripheral venous pressure and exercise in heart disease (ab.), 502
Peritonitis, ACTH, cortisone and chemotherapy in (ab.), 497
Physiology of gastric secretions, 453
Pitressin, urine concentration tests with (ab.), 654
Pituitary adrenocortical system in pancreatic hyperinsulinism (ab.), 92
Plasma
  blood volume expansion with (ab.), 502
  components affecting prothrombin conversion, 255
  thromboplastin component deficiency (ab.), 90
Pneumonia, chloramphenicol in (ab.), 643
Poliomyelitis, bulbar-pharyngeal, deglutition in (ab.), 91
Polyarteritis nodosa with leukemoid reaction (CPC), 487
Porphyria, acute, urinary chromogens in (ab.), 92
Potassium
  content, exchangeable, of women (ab.), 640
  loss with ACTH and cortisone (ab.), 640
Prantal, effects of (ab.), 645
Pregnancy
  hemorrhage during, 111
  toxemias of, and veratrum viride (ab.), 643
Pressures in digestive tract, 73
Priscoline, effects of, in peripheral vascular disease (ab.), 644
Procaine
  amide, intramuscular use of, 145
  and cerebral blood flow (ab.), 106
Progressive visual loss, right-sided weakness and sudden death (CPC), 227
Pronestyl, intramuscular use of, 145
Protein
  deficient diets and S^{35}-cystine (ab.), 97
  flocculation reactions, 730
  metabolic abnormality of nephrotic syndrome (ab.), 97
Proteinuria in renal disease (ab.), 499
Prothrombin, conversion of, 255
Pseudomonas aeruginosa and antibiotics (ab.), 654
Pulmonary
  blood volume and dye dilution method (ab.), 642
  function, vital capacity test of, 809
Pyrogens, bacterial, fate of (ab.), 646

Subject Index

Radioactive
sulfate and extracellular fluid volume (ab.), 107
tagged albumin, disappearance of, in cirrhosis (ab.), 653
Redox reaction of leukocytes in disseminated lupus erythematosus (ab.), 107
Regitine, studies on (ab.), 650
Renal
disease, acid-base changes in, 183
disease, proteinuria in (ab.), 499
excretion of sodium chloride after circulatory stresses (ab.), 102
hemodynamics, effect of nor-epinephrine on (ab.), 648
medullary necrosis, 322
transplants, homogenous, after nephrectomy (ab.), 649
Respiratory disease, acid-base changes in, 183
Retinal vessels, response of, to blood oxygen tension (ab.), 652
Rheumatic
and non-rheumatic families, survey of, 400
fever, cell membrane defect in (ab.), 640
Rickettsialpox, 413
Rocky Mountain spotted fever, cortisone and chloramphenicol in (ab.), 653
Roentgen diagnosis in bleeding from gastrointestinal tract, 713
Rupture of echinococcic cysts into bile ducts, 384

Saccharated iron oxide, intravenous, effects of (ab.), 501
Secretions, gastric, physiology of, 453
Semen, human, fructolysis index in (ab.), 90
Seminars on gastrointestinal physiology
a physiologic and clinical consideration of the pressures developed in the digestive tract, 73
current views on the physiology of the gastric secretions, 453
motility of the alimentary canal in man, 328
neural regulation of gastric and intestinal motility, 209
problems in ulcerative colitis, 760
quantitative tests of gastrointestinal function, 465
the problem of peptic ulcer, 615
Serum
cholinesterase in liver disease and malignancy (ab.), 110
potassium patterns in anuria and oliguria (ab.), 503
Sodium, chloride and potassium content of sweat (ab.), 641
Southern Society for Clinical Research, abstracts of annual meeting, January 19, 1952, 640
Splanchnic blood flow and splanchnic metabolism (ab.), 649
Spleen, intra-arterial epinephrine into (ab.), 504
Splenorenal vein anastomosis and renal function, 242
Steroid excretion, diurnal variation of, in heart failure and cirrhosis (ab.), 93
Subacute bacterial endocarditis (reprint), 544
of tricuspid value due to Micrococcus pyogens (CPC), 82
Sulfur metabolism, studies in (ab.), 97

Testis, effect of testosterone on (ab.), 98
Testosterone, effect of, on testis (ab.), 98
Thermodynamic, kinetic and biologic stability (E.), 251
Thrombo-angiitis obliterans (reprint), 526
Thrombocytopenia, hemostatic defect in, 12
effect of ACTH and cortisone on, 21
Thrombocytopenic purpura
thrombotic, 3, 294, 374
Thrombosis
of arterioles and capillaries (reprint), 567
of internal carotid artery (ab.), 652
Thyroid disorders, radioactivity of blood with I^{131} in, 725
Thyrotrophic hormone, experiences with (ab.), 100
Toxemias of pregnancy and veratrum viride (ab.), 643
Tracer doses of I^{131} in thyroid disorders, 725
Treatment
failure with penicillin, 389
of obesity, 478
Triethylene melamine
in cancer, 428
in malignancy (ab.), 650
Tritium-labeled water in study of ascitic fluid, 668
Tuberculosis, ACTH, cortisone and chemotherapy in (ab.), 504
Tumor, cerebellar, and Cushing's syndrome, 247

Ulcer gastric and duodenal, gastrectomy for (reprint), 575
peptic, effects of prantal in (ab.), 645
problem of, 615
Urine concentration tests with pitressin (ab.), 654
Urobilin, dextrorotatory, after use of antibiotics (ab.), 109

Valvulotomy and mitral stenosis (ab.), 642
Vasodilation produced by sympathectomy (ab.), 644
Vasospasm (ab.), 103
Vectorcardiogram, normal spatial (ab.), 104
Vitamin A tolerance and fat absorption (ab.), 648
Vitamin B_{12} in pernicious anemia, 284

Western Society for Clinical Research, abstracts of annual meeting, January 25, 1952, 90
Wolff-Parkinson-White Syndrome (E.), 121

The American Journal of Medicine

Editor ALEXANDER B. GUTMAN, M. D.
Professor of Medicine
COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK
DIRECTOR OF MEDICAL RESEARCH AND PHYSICIAN TO THE MOUNT SINAI HOSPITAL, NEW YORK

ADVISORY BOARD

DAVID P. BARR, M.D., *Professor of Medicine*, Cornell University Medical College, *New York;* ARTHUR L. BLOOMFIELD, M.D., *Professor of Medicine*, School of Medicine, Stanford University, *San Francisco;* EUGENE A. STEAD, JR., M.D., *Professor of Medicine*, School of Medicine, Duke University, *Durham;* JOSEPH T. WEARN, M.D., *Professor of Medicine*, School of Medicine, Western Reserve University, *Cleveland.*

ASSOCIATE EDITORS

HERRMAN L. BLUMGART, M.D., *Boston;* HARRY GOLD, M.D., *New York;* A. MCGEHEE HARVEY, M.D., *Baltimore;* GEORGE H. HOUCK, M.D., *Palo Alto;* CHESTER S. KEEFER, M.D., *Boston;* T. GRIER MILLER, M.D., *Philadelphia;* WALTER L. PALMER, M.D., *Chicago;* OSWALD H. ROBERTSON, M.D., *Stanford;* EPHRAIM SHORR, M.D., *New York;* GEORGE W. THORN, M.D., *Boston;* WILLIAM S. TILLETT, M.D., *New York;* ROY H. TURNER, M.D., *New Orleans;* RUSSELL M. WILDER, M.D., *Bethesda, Md.;* M. M. WINTROBE, M.D., *Salt Lake City;* W. BARRY WOOD, M.D., *St. Louis;* JOHN B. YOUMANS, M.D., *Nashville.*

Volume XIII
JULY TO DECEMBER
1952

THE AMERICAN JOURNAL OF MEDICINE, INC.
NEW YORK MCMLII

CONTENTS OF VOLUME XIII
ORIGINAL ARTICLES

Disorders of the Blood in Disseminated Lupus Erythematosus	*C. Lockard Conley*	1
Thrombotic Thrombocytopenic Purpura	*Benjamin R. Gendel*, *Joseph M. Young*, *Alfred P. Kraus*	3
Hemostatic Defect in Thrombocytopenia as Studied by the Use of ACTH and Cortisone	*William W. Faloon*, *Richard W. Greene*, *Eugene L. Lozner*	12
Effect of Corticotropin (ACTH) and Cortisone on Idiopathic Thrombocytopenic Purpura	*Sloan J. Wilson*, *Gustave Eisemann*	21
Hypercoagulability of the Blood of Patients with Hepatic Cirrhosis Following Administration of ACTH	*William J. Eisenmenger*, *Robert J. Slater*, *Alfred M. Bongiovanni*	27
Chronic Hypoplastic Neutropenia	*Theodore H. Spaet*, *William Dameshek*	35
Mediterranean Hemopathic Syndromes (Cooley's Anemia) in Adults. Study of a Family with Unusual Complications	*Harold W. March*, *Samuel M. Schlyen*, *Samuel E. Schwartz*	46
Circulating Blood Eosinophils in Acute Infectious Disease and Eosinopenic Response	*H. A. Weiner*, *Dimitry Morkovin*	58
A Physiologic and Clinical Consideration of the Pressures Developed in the Digestive Tract	*J. P. Quigley*, *Daniel A. Brody*	73
Fever of Unknown Origin		82
The Western Society for Clinical Research—Abstracts of Papers Presented at the Fifth Annual Meeting, Carmel, California, January 25 and 26, 1952		90
American Federation for Clinical Research—Abstracts of Papers Presented at the Southern Sectional Meeting Held in Atlanta, Georgia, January 18, 1952		103
Hemorrhagic State during Pregnancy. With the Presence of Maternal Rh Antibodies, Death of the Fetus and Hypofibrinogenemia	*Oscar D. Ratnoff*, *Carl F. Lauster*, *John G. Sholl*, *Myron O. Schilling*	111
The Wolff-Parkinson-White Syndrome and Related Phenomena	*Myron Prinzmetal*	121
Difference in the Relation of Cardiac to Emetic Actions in Oral and Parenteral Digitalization	*Harry Gold*, *Theodore Greiner*, *McKeen Cattell*, *Walter Modell*, *Joseph Gluck*, *Raymond Marsh*, *Sydney Mathes*, *Dean Hudson*, *Donald Robertson*, *Leon Warshaw*, *Harold Otto*, *Nathaniel Kwit*, *Milton Kramer*	124

Intramuscular Use of Pronestyl (Procaine Amide)	*Samuel Bellet, Stanley E. Zeeman, Stanton A. Hirsh*	145
Infectious Mononucleosis	*Colonel Robert J. Hoagland.*	158
Infectious Mononucleosis. The Value of Differential Absorption Tests in Its Serologic Diagnosis	*Sidney Leibowitz*	172
Clinical-chemical Studies of Acid-base Abnormalities. Changes in Acid-base Balance Observed in Renal and Respiratory Disease	*A. Yeomans, G. H. Stueck, Jr.*	183
Neural Regulation of Gastric and Intestinal Motility	*W. B. Youmans*	209
Progressive Visual Loss, Right-sided Weakness and Sudden Death		227
Infectious Mononucleosis. Report of Case with First Appearance of Significant Numbers of Heterophil Antibodies and Abnormal Lymphocytes ("Virocytes") in Seventh Week of Illness	*Hyman Bakst, Sidney Leibowitz*	235
Effects of Unilateral Renal Vein Hypertension Secondary to Splenorenal Vein Anastomosis on Individual Kidney Function	*Jonas H. Sirota, Robert A. Nabatoff*	242
Coexistence of Cushing's Syndrome and Internal Hydrocephalus Produced by a Cerebellar Tumor	*K. R. Crispell, William Parson*	247
Thermodynamic, Kinetic and Biologic Stability	*DeWitt Stetten, Jr.*	251
Parahemophilia in Three Siblings (Owren's Disease). With Studies on Certain Plasma Components Affecting Prothrombin Conversion	*Benjamin Alexander, Robert Goldstein*	255
Limit of Hemoglobin Synthesis in Hereditary Hemolytic Anemia. Its Relation to the Excretion of Bile Pigment	*Lt. Col. William H. Crosby, Lt. Col. Joseph H. Akeroyd.*	273
Prolonged Treatment of Pernicious Anemia with Vitamin B_{12}	*C. Lockard Conley, Thomas W. Green, Robert C. Hartmann, Julius R. Krevans*	284
Thrombotic Thrombocytopenic Purpura. Review of the Literature and Report of Three Cases	*Jeremiah A. Barondess*	294
Incidence of Leukemia in Survivors of the Atomic Bomb in Hiroshima and Nagasaki, Japan	*Jarrett H. Folley, Wayne Borges, Takuso Yamawaki*	311
Renal Medullary Necrosis	*E. E. Mandel*	322
Motility of the Alimentary Canal in Man. Review of Recent Studies	*Charles F. Code, Nicholas C. Hightower, Jr., Carl G. Morlock*	328
Antigen-antibody Reactions		352
Acromegaly, Mandibular Tumor and Pyrexia		366
Thrombotic Thrombocytopenic Purpura. Confirmation of Clinical Diagnosis by Bone Marrow Aspiration	*Talbert Cooper, J. M. Stickney, Gertrude L. Pease, Warren A. Bennett*	374
Rupture of Echinococcus Cysts into the Bile Ducts Simulating Stones in the Common Duct	*Donald H. Atlas, Harold Kamenear*	384
Fainting	*Eugene A. Stead, Jr.*	387

Experimental Approach to the Problem of Treatment Failure with Penicillin. I. Group A Streptococcal Infection in Mice	*Harry Eagle*	389
A Long-term Survey of Rheumatic and Non-rheumatic Families. With Particular Reference to Environment and Heredity	*Frieda G. Gray*, *Robert W. Quinn*, *Julia P. Quinn*	400
Rickettsialpox. Report of Four Apparent Cases in Pennsylvania	*Alfred C. LaBoccetta*, *Harold L. Israel*, *Angelo M. Perri*, *M. Michael Sigel*	413
Octamethyl Pyrophosphoramide in the Therapy of Myasthenia Gravis	*Capt. Lloyd Gregory, Jr.*, *E. D. Futch*, *C. T. Stone*	423
Triethylene Melamine in Clinical Cancer Chemotherapy	*Alfred Gellhorn*, *Morton M. Kligerman*, *Israeli Jaffe*	428
Alcaptonuria and Ochronosis. With a Report of Three Patients and Metabolic Studies in Two	*Morton Galdston*, *J. Murray Steele*, *Konrad Dobriner*	432
Current Views on the Physiology of the Gastric Secretions	*Franklin Hollander*	453
Quantitative Tests of Gastrointestinal Function	*Henry D. Janowitz*	465
Treatment of Obesity		478
Leukemoid Reaction, Abdominal Pain and Mesenteric Lesions		487
American Federation for Clinical Research—Abstracts of Papers Presented at the Western Sectional Meeting in Carmel, California, January 24, 1952		496
Familial Mediterranean (Cooley's) Anemia Complicated by Chronic Hepatitis. Results of Treatment with ACTH	*Edwin Englert, Jr.*, *Leon J. Warshaw*	507
Foreword	*George Baehr*	517
Founding and Early Days of the Mount Sinai Hospital	*Eli Moschcowitz*	519
Thrombo-angiitis Obliterans: A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene	*Leo Buerger*	526
An Acute Infectious Disease of Unknown Origin. A Clinical Study Based on 221 Cases	*Nathan E. Brill*	533
Removal of Neoplasms of the Urinary Bladder. A New Method, Employing High-frequency (Oudin) Currents through a Catheterizing Cystoscope	*Edwin Beer*	542
A Study of the Endocardial Lesions of Subacute Bacterial Endocarditis, with Particular Reference to Healing or Healed Lesions; with Clinical Notes	*E. Libman*	544
Blood Transfusion by the Citrate Method	*Richard Lewisohn*	550
Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation	*Albert A. Epstein*	556
The Nonoperative Determination of Patency of Fallopian Tubes. By Means of Intrauterine Inflation with Oxygen and the Production of an Artificial Pneumoperitoneum	*I. C. Rubin*	562
An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries. An Undescribed Disease	*Eli Moschcowitz*	567

Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen. A Hitherto Undescribed Type	*N. E. Brill* *George Baehr* *Nathan Rosenthal*	570
The Mortality and Late Results of Subtotal Gastrectomy for the Radical Cure of Gastric and Duodenal Ulcer	*Albert A. Berg*	575
Regional Ileitis. A Pathologic and Clinical Entity	*Burrill B. Crohn* *Leon Ginzburg* *Gordon D. Oppenheimer*	583
A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis)	*George Baehr* *Paul Klemperer* *Arthur Schifrin*	591
The Natural History of Cushing's Syndrome	*Charles M. Plotz* *Abbie I. Knowlton* *Charles Ragan*	597
The Problem of Peptic Ulcer	*Joseph B. Kirsner* *Walter L. Palmer*	615
Southern Society for Clinical Research—Abstracts of Papers Presented at the Sixth Annual Meeting, Atlanta, Georgia, January 19, 1952		640
American Mucocutaneous Leishmaniasis Successfully Treated with 2-Hydroxystilbamidine	*I. Snapper*	655
Basis for Dietary Treatment in the Prevention and Control of Atherosclerosis	*David P. Barr*	665
Quantitative Studies of Ascitic Fluid Circulation with Tritium-labeled Water	*Theodore C. Prentice* *William Siri* *Ethel E. Joiner*	668
Experience with Needle Liver Biopsies at the Hepatitis Center for Japan and Korea, 1950–1951	*Capt. Stephen H. Deschamps* *Lt. Col. Arthur Steer*	674
An Evaluation of Needle Biopsy of the Liver	*Edward R. Christian*	689
Altered Liver Function of Chronic Congestive Heart Failure	*John M. Evans* *Hyman J. Zimmerman* *J. Grant Wilmer* *Lawrence E. J. Thomas* *Clayton B. Ethridge*	704
Early Roentgen Diagnosis in Massive Bleeding from the Upper Gastrointestinal Tract. I. Clinical Evaluation of Safety and Reliability of the Method in 123 Patients	*Norman Zamcheck* *Thomas P. Cotter* *Simon E. Hershorn* *Thomas C. Chalmers* *Max Ritvo* *Franklin W. White*	713
Blood Levels after Tracer Doses of Radioactive Iodine in the Diagnosis of Thyroid Disorders	*Solomon Silver* *Mack H. Fieber* *Stephen B. Yohalem*	725
Protein Flocculation Reactions. A Physico-chemical Approach	*Abraham Saifer*	730
Current Principles of Management in Gout	*Alexander B. Gutman* *T. F. Yü*	744
Problems in Ulcerative Colitis	*Thomas E. Machella*	760
Hyperventilation in a Patient Who Stammered		777
Aplastic Anemia in a Patient Receiving Chloramphenicol		782

Autoimmune Hemolytic Diseases and Cryoglobulinemia Associated with Chronic Lymphocytic Leukemia. Hematologic and Metabolic Studies . . . . . *Albert B. Craig, Christine Waterhouse, Lawrence E. Young* . . . 793

Coarctation of the Aorta in Infancy. Report of Two Cases with Death from Left Ventricular Failure . . . . *H. Milton Rogers, Councill C. Rudolph, John H. Cordes, Jr.* . . . 805

Inspiratory-Expiratory Vital Capacity Test of Pulmonary Function . . . . . *Alan Leslie* 809

COPYRIGHT, 1952
BY THE AMERICAN JOURNAL OF MEDICINE, INC.
All Rights Reserved

Printed in the United States of America

for more efficient oral absorption of androgen

ORETON-M

buccal tablets

Maximum absorption and utilization of methyltestosterone is more certain when ORETON-M Buccal Tablets are prescribed. ORETON-M Buccal Tablets contain the hormone predissolved in POLYHYDROL® base, a solid solvent that is itself soluble in saliva An active transfer agent, POLYHYDROL facilitates absorption of steroids from tablets into mucosal capillaries. ***Most convenient*** intraoral type tablet available, ORETON-M® (Methyltestosterone U.S.P.) Buccal Tablets permit patients to talk, smoke, and swallow without loss of active material.

ORETON-M

Schering CORPORATION • BLOOMFIELD, N. J.

IN CANADA: SCHERING CORPORATION, LTD., MONTREAL

a *new* experience in *tranquillity*

for anxious, tense, restless patients

Seconesin

safe relaxant-sedative

Seconesin introduces a totally new idea in sedation... a safe, non-narcotic, rapid method to bring "a classical state of relaxation," a feeling of being pleasantly and comfortably at ease in tense, restless, anxious, wound-up patients.

each lime-colored, scored tablet combines:

MEPHENESIN 400 mg.
modern relaxant of choice • Council Accepted
and
SECOBARBITAL 30 mg.
tried and true sedative • Council Accepted

Seconesin is safer because its euphoric influence is attained with a minimum of secobarbital... and because both its components are rapidly dissipated and eliminated. No fear of cumulation or "hangover."

Daytime relaxation with **Seconesin** is so calming that most patients ***sleep well at night*** without hypnotics.

Average dose: 1 Seconesin tablet every 4 hours; 1 or 2 on retiring but this is usually not necessary. Supplied on your Rx in bottles of 50, 100 and 500 tablets.

samples (perhaps for personal trial) and literature on request.

CROOKES LABORATORIES, INC. Crookes MINEOLA, NEW YORK

Seconesin, trademark

Therapeutic Preparations for the Medical Profession

EDIOL
Trademark

[ORAL FAT EMULSION SCHENLEY]

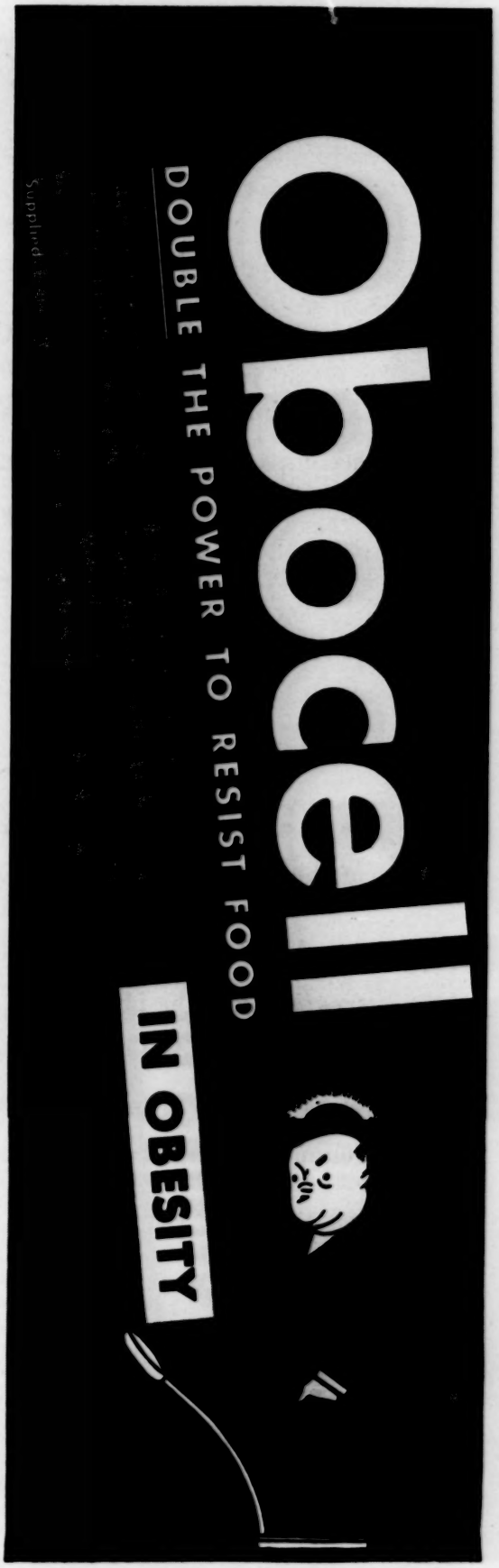
- **provides extra calories**—150 per ounce, in easily utilized form, for quick gain in weight and strength
- **without excessive bulk**—no undue digestive burden...no reduction in appetite for other foods
- **or cloying taste**—delicious alone or with a variety of nutritious foods

In 16-oz. bottles.

SCHENLEY LABORATORIES, INC.
LAWRENCEBURG, INDIANA

Schenley

© Schenley Laboratories, Inc.



Concerning

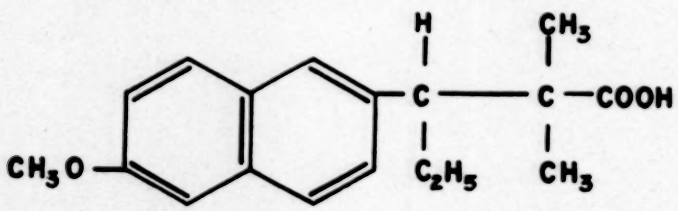
VALLESTRIL*...

(BRAND OF METHALLENESTRIL)

A NEW PRODUCT

Clinical evidence indicates that much estrogen therapy is accompanied by a high incidence of unfortunate side actions such as withdrawal bleeding, nausea and edema.

G. D. Searle & Co. presents VALLESTRIL.....



as an effective estrogenic substance with a *strikingly low incidence* of these undesirable side effects.

VALLESTRIL is available in 3 mg. scored tablets. For treatment of the physiologic or artificial menopause—3 mg. (one tablet) twice daily for two weeks. Then a maintenance dose of one tablet daily for an additional month or longer if symptoms require continued administration.

*Trademark of G. D. Searle & Co.

SEARLE RESEARCH IN THE SERVICE OF MEDICINE

New aureomycin minimal dosage for adults —four 250 mg. capsules daily, with milk.

READING ROOM, COOLIDGE CORNER BRANCH, BROOKLINE, MASS. PUBLIC LIBRARY

a most widely accepted antibiotic in the broad-spectrum field is

AUREOMYCIN

Hydrochloride Crystalline

because

Physicians in the United States and throughout the world have recognized the time-saving value of immediate use of aureomycin in cases of active infection.

The successful use of aureomycin, as described in publications by physicians throughout the world, has increasingly encouraged others to use this antibiotic and publish reports thereon. To date, more than 7,000 original reports, editorials, brief comments, and similar notations have appeared in the published literature.

The trend of the literature clearly indicates that in desperate situations caused by infection, where previously cure would have proved difficult or impossible, aureomycin has saved the day.

Capsules: **50 mg.—Vials of 25 and 100. 100 mg.—Vials of 25 and bottles of 100. 250 mg.—Vials of 16 and bottles of 100.**
Ophthalmic Solution: **Vials of 25 mg.; solution prepared by adding 5 cc. distilled water.**

LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID COMPANY
30 Rockefeller Plaza, New York 20, N.Y.

INDISPUTABLE PROOF of an INDISPENSABLE SERVICE

New 5TH MODERN DRUG

AND THERAPEUTIC

IN *REGULAR USE* BY 91% OF ALL DOCTOR

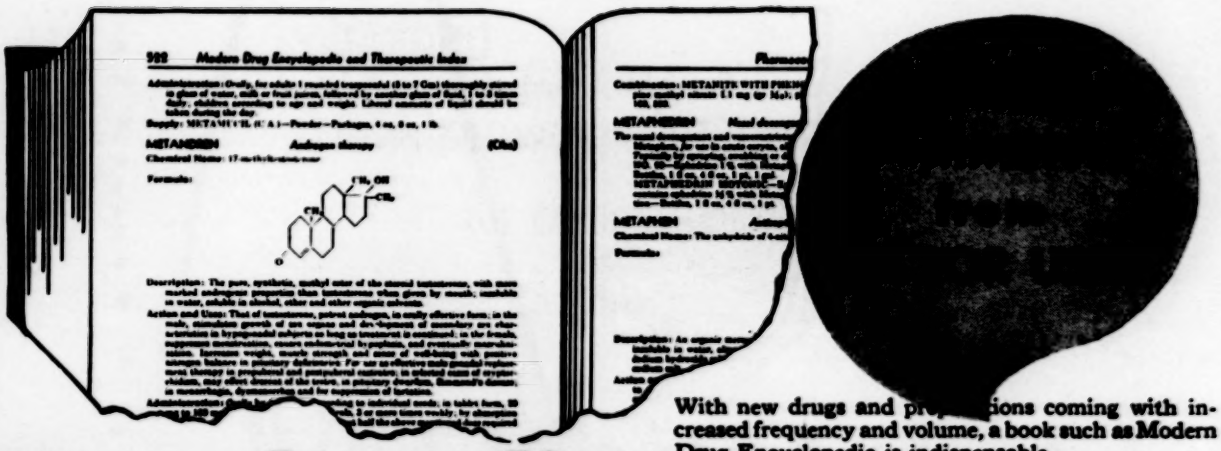
Dramatic proof of the finger tip reference value of THE MODERN DRUG ENCYCLOPEDIA and its bi-monthly supplementary service, MODERN DRUGS, comes direct from 3,000 of their 50,000 doctor and druggist users. Results of an independently* conducted reader-research effort show overwhelming dependence upon this quick reference service—complete from description to prescription for authoritative data on new ethical drugs. Com-

THE MODERN DRUG ENCYCLOPEDIA
is handsomely bound in red fabricoid. Contains 1500 pages, size 6" x 9¼" x 2¼". POSTPAID, $15** U.S.A.; $18 FOREIGN

MODERN DRUGS SUPPLEMENTS
are sent (beginning Jan. 1953) bi-monthly **FREE** to every encyclopedia subscriber. Keeps you up-to-date between editions. Complete with cumulative index for accurate reference to all new products therapeutically and alphabetically.

DRUG PUBLICATIONS, INC.

49 West 45th Street, New York 36, New York



Encyclopedia

INDEX

AND DRUGGIST SUBSCRIBERS

pletely rewritten, the new 5th Edition of THE MODERN DRUG ENCYCLOPEDIA lists nearly 4,000 ethical drugs (including 1,500 brand new listings) of 175 manufacturers. Each listing includes latest composition, action, use, supply, dosage, caution and contra-indication of the drug. Here is data that you, too, will find indispensable for saving time, without sacrifice of an authoritative source.

FINGER TIP DESCRIPTIONS AUTHORITATIVELY COMPILED IN SEVEN SPECIAL SECTIONS

- Drugs
- Biologicals
- Allergens
- General Index
- Therapeutic Index
- Manufacturer's Index

featuring for the first time

- Self Pronouncing Drug Listings Generic Name Index

*AUDIENCE ANALYSTS, Phila., Pa.

With new drugs and pro[illegible]ions coming with increased frequency and volume, a book such as Modern Drug Encyclopedia is indispensable.

New York, New York

I have owned every edition of your encyclopedia except the first. Would have bought it but did not know this book was printed. If the physicians of this country and Canada and some of the foreign countries knew its value, you would have been able to sell twice as many or more books per year.

Memphis, Tennessee

I like Modern Drugs because it gives honest pharmacological information; because it frequently gives contra-indications and dangers; because it describes members of a similar group in similar or identical terms. I would find it hard to practice without it.

Green Bay, Wis.

I have Modern Drug Encyclopedia and use the journal as supplement, thus at my finger tips I have information on new drugs.

York, Pa.

I don't see how a physician can know what other physicians prescribe for patients without this. It is an almost indispensable (not quite) adjunct to my practice.

Washington, D.C.

I find the bound book (present 5th Edition) most valuable.

White Plains, N.Y.

One of my most valuable books and used more often than any other that I have.

Lincolnton, N.C.

DRUG PUBLICATIONS, INC.
49 West 45th Street, New York 36, New York

Enclosed is the sum of fifteen dollars ($15**U.S.A.) for which please send me postpaid the new Fifth Edition of THE MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX and MODERN DRUGS. (New York City residents please add 3% for sales tax.)

NAME _____ M.D.

ADDRESS _____

CITY _____ ZONE _____ STATE _____

**Includes three-year supplementary service at $3 per year.

Same hard candy form as Pondets

Easy to take—pleasant tasting

Now . . . . .

Sul-Pondets

Sulfa *plus* antibiotics

Affording the combined therapeutic advantages of:

2 potent antibiotics

★ *Penicillin* (20,000 units)

★ *Bacitracin* (50 units)

efficient penicillin—potentiating sulfonamide

★ *Sulfadiazine* (2 grains)

highly active topical anesthetic

★ *Benzocaine* (3 mg.)

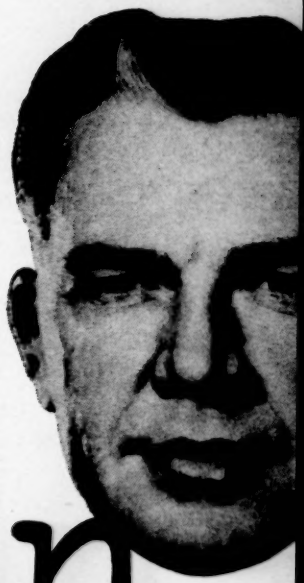
Supplied: Jars of 36 troches

Sul-Pondets®

PENICILLIN — BACITRACIN — SULFADIAZINE

Troches with Benzocaine

Wyeth®



combined

estrogen-androgen therapy

for chronic hormone

deficiency states

Menagen®

with Methyltestosterone

(oral estrogen-androgen, Parke-Davis)

In such chronic hormone deficiency states as the female or male climacteric, estrogen-androgen combination enhances the desired therapeutic response while neutralizing unwanted side actions.

Especially effective in the metabolic and constitutional spheres, MENAGEN WITH METHYLTESTOSTERONE provides specific advantages for the relief of menopausal symptoms:

- additive action for better symptomatic relief
- optimum sense of well-being
- greater effect in neurotic patients than estrogen alone
- minimizes both estrogenic and androgenic side effects
- contains naturally derived estrogen; therefore, well tolerated
- orally effective and economical

Packaging: MENAGEN WITH METHYLTESTOSTERONE: in bottles of 100 capsules. Each capsule contains MENAGEN equivalent to the estrogenic activity of 10,000 I. U. ketohydroxyestratriene, and 10 mg. methyltestosterone.

Parke, Davis & Company

A drug of choice in tuberculosis

As therapeutically active as streptomycin, CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK is less toxic to the vestibular apparatus, minimizes pain and swelling on injection, and may be used even in some patients allergic to streptomycin.

This preferred product is available in dry powder form and in convenient ready-to-inject form as SOLUTION OF CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK.

PARA-AMINOSALICYLIC ACID MERCK (PAS), when used in combination with CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK, prolongs the effective period of antibiotic therapy by inhibiting or delaying the development of bacterial resistance.

Crystalline Dihydrostreptomycin Sulfate Merck

COUNCIL ACCEPTED

Research and Production for the Nation's Health

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY
In Canada: MERCK & CO. Limited—Montreal

in functional G.I. *distress*

though findings are negative, patients remain positive of their many symptoms—belching, flatulence, nausea, indigestion and constipation.

prompt and effective relief

can be given most of these patients by prescribing *Decholin/Belladonna* for alleviating spasm and stimulating liver function.

DECHOLIN® with BELLADONNA

reliable spasmolysis

The belladonna component of *Decholin/Belladonna* effectively relieves pain due to spasm and incoordinate peristalsis, and facilitates biliary and pancreatic drainage through relaxation of the sphincter of Oddi.

improved liver function

Dehydrocholic acid *(Decholin)*, the most powerful *hydro*choleretic known, increases bile flow, flushes the biliary tract with thin fluid bile and provides mild laxation without catharsis.

DOSAGE

One or, if necessary, two *Decholin/Belladonna* Tablets three times daily.

COMPOSITION

Each tablet of *Decholin/Belladonna* contains *Decholin* (brand of dehydrocholic acid) 3¾ gr., and ext. of belladonna, 1/6 gr. (equivalent to tincture of belladonna, 7 minims). Bottles of 100.

AMES AMES COMPANY, INC · ELKHART, INDIANA
Ames Company of Canada, Ltd., Toronto

DB-1

only one application of EURAX® blocks the *"itch-scratch reflex"* for 6 to 8 hours

The prompt, prolonged and effective action of the new antipruritic, EURAX, has been authoritatively reported in leading dermatologic journals.[1-5]

EURAX affords "complete relief" in two out of every three cases and "considerable relief" in the majority of the remainder.[1] Not an antihistaminic, not a -caine derivative . . . EURAX is virtually nonsensitizing and nontoxic,[1-3] and, importantly, does not lose its effectiveness after continued use.[2]

In addition to its nonspecific antipruritic properties, EURAX is a potent scabicide.[6-11] Only 1-2 applications produce cure rates ranging up to 100 per cent with the added advantage that the bacteriostatic properties of EURAX effectively control secondary coccal infections.

EURAX . . . the new long-lasting antipruritic

EURAX (brand of crotamiton) contains N-ethyl-o-crotonotoluide* in a 10 per cent concentration in a vanishing cream base.

Tubes of 20 Gm. and 60 Gm. and jars of 1 lb.

bibliography: (1) Couperus, M.: J. Invest. Dermat. *13*:35, 1949. (2) Peck, S. M., and Michelfelder, T. J.: New York State J. Med. *50*:1934, 1950. (3) Soifer, A. A.: Quart. Rev. Int. Med. & Dermat. *8*:1, 1951. (4) Johnson, S. M., and Bringe, J. W.: Arch. Dermat. & Syph. *63*:768, 1951. (5) Hitch, J. M.: Clinical Appraisal of a New Antipruritic (N-ethyl-o-crotonotoluide), to be published. (6) Tobias, N.: G. P. *4*:43, 1951. (7) Domenjoz, R.: Schweiz. med. Wchnschr. *76*:1210, 1946. (8) Patterson, R. L.: South. M. J. *43*:449, 1950. (9) Pierce, H. E., Jr.: J. Nat. M. A. *43*:107, 1951. (10) Hand, E. A.: J. Michigan M. Soc. *49*:1286, 1950. (11) Tronstein, A. J.: Ohio State M. J. *45*:989, 1949.

*U.S. Pat. #2,505,681

E-43

Geigy **GEIGY PHARMACEUTICALS** • Division of Geigy Company, Inc.
220 Church Street, New York 13, New York

90-Second Asthma Relief

Lasting 4 Hours!

NEW! Relay Action in One Tablet . . .

You can now prescribe immediate-acting, sublingual aludrine (n-isopropylarterenol HCl) *and* the classic theophylline-ephedrine-phenobarbital anti-asthmatic triad in a single tablet. The asthma patient simply places a *Nephenalin* tablet under the tongue until the purple sugar coating is dissolved, then swallows the nucleus.

Aludrine (n-isopropylarterenol HCl) in the coating, absorbed sublingually, exerts pronounced bronchodilator action within 90 seconds. The nuclear combination of theophylline, ephedrine and phenobarbital is absorbed enterically to *relay* and *extend* the initial asthma relief for at least four hours. The average asthma patient may thus abort or suppress symptoms for a whole day with as few as three *Nephenalin* tablets!

Nephenalin®

Anti-asthmatic Tablets

Thos. Leeming & Co. Inc., 155 East 44th St., New York 17, N.Y.

Gentlemen: Please send me samples of Nephenalin, your new relay-action anti-asthmatic tablet.

Name_____

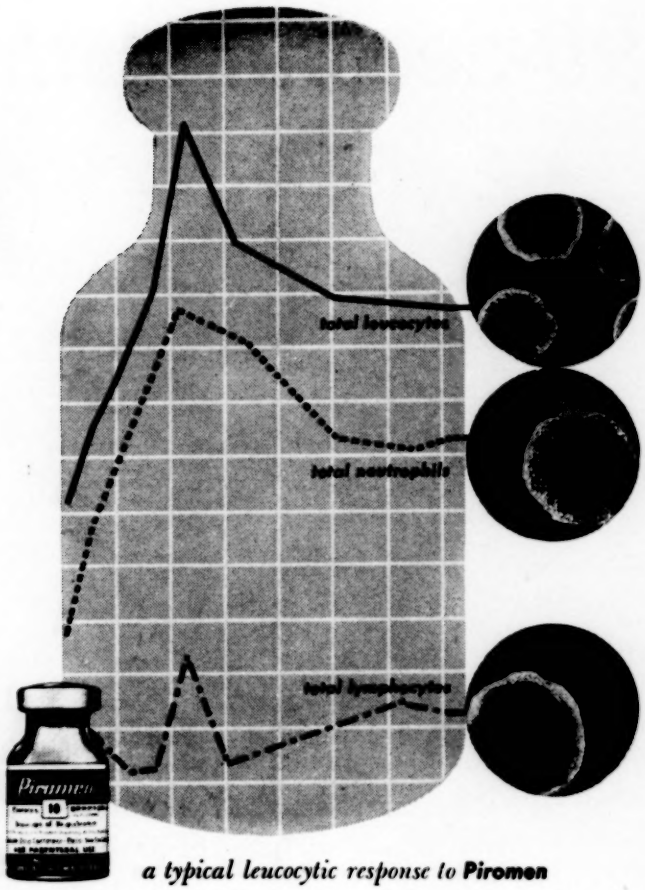
Street_____

City_____ Zone_____ State_____ C

Piromen*

(DISPERSION OF DESACCHROMIN)

for effective control of a wide variety of *ALLERGIES* and *DERMATOSES*



a typical leucocytic response to **Piromen**

Every day more physicians are discovering the early clinical benefits effected by the administration of ***Piromen,*** employed either as a specific, or concomitantly with other drugs.

Piromen is a biologically-active bacterial polysaccharide which produces a marked leucocytosis and a stimulation of the reticulo-endothelial system. It is nonprotein, nonantigenic, and may be employed safely within a wide range of dosage.

Piromen is prepared in stable colloidal dispersion for parenteral use. It is supplied in 10 cc. vials containing either 4 gamma (micrograms) per cc., or 10 gamma per cc.

For a comprehensive booklet detailing the use of this new therapeutic agent, merely write "***Piromen***" on your *Rx* and mail to—

*TRADE MARK

Manufactured by

TRAVENOL LABORATORIES, INC.

Subsidiary of BAXTER LABORATORIES, INC., MORTON GROVE, ILLINOIS